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New technologies applied to diabetes

Thematic Meeting organized by the French Society for Diabetes

Paris, Institut Pasteur, December the 16th, 2011

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Nouvelles technologies appliquées au diabète
Journée thématique organisée par la Société Francophone du Diabète

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Editorial

Technologies applied to diabetes

Les technologies appliquées au diabète

André Malraux said: "I think that the task for the next century, in front of the most terrible threat that mankind knew, will be to integrate gods". We, humble diabetes-care providers, are convinced that the technologies, like the *Deus ex machina,* will have to be more and more integrated into the management of diabetes. In fact, it is likely that no other pathology is as hard to model as diabetes, and the Lord's help will be most welcome. However, we have succeeded, after about 40 years, in moving from glass syringes that needed to be sterilized before each injection of insulin of animal origin, the dosage of which was based upon a urine glucose test, to the first models of artificial beta cells working in a closed-loop mode and, recently, outside of the hospital setting. Nevertheless, the task remains difficult because we are not only treating blood glucose values, but human beings, including their physical, psychological and social complexities. Technological devices (such as pumps, sensors, stimulators, algorithmic software and newly launched micro-PCs) are still needed to restore lost physiological functions in a safe, efficient and manageable everyday way. The final challenge is even greater: to restore the freedom to plan activities, free of worries, with passion and enthusiasm, to patients who are often tired of being patient. This special issue, which is associated with the theme of SFD 2011, addresses the technological dimension of treatment because it is necessary, but also the human dimension, because the former on its own is not enough.

Enjoy!

Conflict of interest statement

The author has no conflict of interest in connection to this article.

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External insulin pump treatment in the day-to-day management of diabetes: benefits and future prospectives

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Abstract

The aim of diabetes treatment is to achieve tight glucose control to avoid the development of chronic diabetes complications while reducing the frequency of hypoglycaemic episodes. The main clinical indications of pump therapy in type 1 diabetes are persistently elevated HbA_{1c} in spite of the best attempts of intensified insulin therapy with multiple daily injections (MDI) and/or frequent, disabling or severe hypoglycaemia. Several trials have demonstrated the superiority of continuous subcutaneous insulin infusion (CSII) over MDI, and highlighted the benefits of using short-acting insulin analogues. However, new MDI regimens with long-acting insulin analogues challenge insulin pump therapy in some indications, thus indicating the need for precise selection of those patients who will benefit the most from CSII. In type 2 diabetes, pump therapy may be an invaluable tool in selected patients characterized by chronic elevation of HbA_{1c}, obesity and high insulin requirements. In addition, in any case, specific education, training and ongoing evaluation of the benefit/risk ratio of the treatment are mandatory. Furthermore, there is continuing progress in the development of pump and catheter features, and insulin kinetics can still be improved. These technical advances are part of the work in progress towards developing closed-loop systems.

Keywords: *External insulin pump; Intensive insulin therapy; HbA_{1c}; Glycaemic control; Diabetes; Review*

Résumé

Intérêts et perspectives du traitement par pompe à insuline externe dans la prise en charge du diabète

Le but du traitement du diabète est d'obtenir un équilibre glycémique satisfaisant afin d'éviter le développement des complications chroniques du diabète et de réduire dans le même temps la fréquence des hypoglycémies. Les principales indications du traitement par pompe dans le diabète de type 1 sont l'augmentation durable de l'HbA_{1c} malgré un traitement intensif bien conduit par injections multiples, et la survenue d'hypoglycémies fréquentes, handicapantes, ou sévères. Plusieurs études ont démontré la supériorité du traitement par pompe par rapport aux injections multiples, et souligné les bénéfices apportés par l'utilisation des analogues de l'insuline rapide. Les nouveaux schémas qui utilisent les analogues longs de l'insuline entrent en compétition avec le traitement par pompe dans certaines indications, soulignant la nécessité d'une sélection précise des patients qui seront les plus grands bénéficiaires du traitement par pompe. Dans le diabète de type 2, le traitement par pompe peut être un outil intéressant chez des patients sélectionnés, caractérisés par un déséquilibre glycémique chronique, une obésité sévère et des besoins en insuline élevés. Dans tous les cas, une éducation spécifique, un entraînement à l'utilisation et une évaluation continue du rapport bénéfice/risque du traitement sont indispensables. Les caractéristiques des pompes et des cathéters sont en évolution permanente, la cinétique des insulines peut être encore améliorée. Ces avancées techniques font partie intégrante des travaux en cours pour le développement de systèmes en boucle fermée.

Mots-clés : Pompe à insuline externe ; Insulinothérapie intensive ; HbA_{1c} ; Contrôle glycémique ; Diabète ; Revue générale

1. Introduction

The goal of type 1 diabetes treatment is to achieve tight glucose control to avoid chronic diabetes complications while limiting the frequency of hypoglycaemic episodes in day-to-day life. Over the past few decades, considerable efforts have been made to improve the tools of treatment. The development of continuous subcutaneous insulin infusion (CSII) and, more recently, short-acting insulin analogues with advantageous pharmacokinetic properties constitute important advances in the treatment of diabetes.

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CSII using external insulin pumps was first introduced in the 1970s as a way of achieving and maintaining strict control of blood glucose concentrations in type 1 diabetes patients [1] through more physiological insulinization than achieved with multiple daily injections (MDI). The exclusive use of soluble short-acting insulin, infused subcutaneously at the same site for 2 or 3 days, reduces the variability of insulin absorption compared with long-acting insulins. CSII also allows greater flexibility of insulin infusion, thanks to the ability to program several basal rates and to adjust meal-time boluses when required. It is noteworthy that the modern intensified insulin regimens, whether delivered by CSII or MDI, all require the implementation of frequent blood glucose self-monitoring, dietary advice and structured diabetes education to improve glycaemic control. Under these conditions, CSII has proved superior to MDI in terms of HbA_{1c}, hypoglycaemic episodes, glucose variability and quality of life in those selected patients who fail to obtain good glycaemic control in spite of an intensified MDI regimen. These findings have also led to the validation by the French Health Authority of insulin pump treatment in patients who fail to obtain good glycaemic control with MDI [2], and to the recent publication of French recommendations for the use of CSII in type 1 and type 2 diabetes patients [3].

2. Benefits of CSII in type 1 diabetes

2.1. HbA_{1c}

Several studies have confirmed the superiority of CSII over MDI in terms of HbA_{1c} [4-7]. In the Diabetes Control and Complications Trial (DCCT) [8], HbA_{1c} levels in the intensive-treatment group were significantly lower with CSII than with MDI (ranging from -0.2% to -0.4%). However, because the patients who were randomly assigned to receive intensive treatment in the DCCT could choose between CSII and MDI (they were not randomly allocated to the type of intensive therapy), the results could be biased. Nevertheless, two recent meta-analyses of trials have compared CSII and MDI regimens, involving 600 and 1547 patients, respectively [9,10], and have reported an overall benefit of CSII over MDI, with a reduction of HbA_{1c} in the range of 0.4-0.5% that was associated with a reduction in insulin requirements. A recent Cochrane review reported a lower mean difference of 0.3% [11], but included studies of very short duration and early trials from the 1980s, when pumps were less reliable and less technically sophisticated.

As all of the trials included in these meta-analyses were performed with human regular insulin, except one study that used insulin lispro [12], it was necessary to investigate whether the introduction of short-acting insulin analogues would modify the relative performances of CSII and MDI. In fact, with either CSII or MDI, the optimal meal-time insulin is a short-acting insulin analogue, as this exhibits pharmacodynamic advantages over human regular insulin, including faster absorption, earlier onset and shorter duration of action.

Several randomized controlled trials have shown that CSII with short-acting insulin analogues is more efficient for postprandial glycaemia and HbA_{1c} concentrations than CSII with human regular insulin [13-15] (Table 1). A meta-analysis also concluded that the use of insulin analogues in pump therapy results in a modest (0.26%), but significant, reduction in HbA_{1c} compared with soluble insulin [16]. The pharmacokinetic properties of short-acting insulin analogues are certainly responsible for this slight superiority, thanks to improvements in postprandial glucose levels and stability.

However, the efficacy of CSII *vs* MDI therapy has been evaluated in only a limited number of randomized controlled trials in which rapid-acting analogues were used for both regimens, with two out of three concluding the superiority of CSII [14,17,18] (Table 2). A pooled analysis of the three studies suggested that CSII is associated with better glycaemic control, particularly in patients with initially suboptimal control [19]. The magnitude of the effect of CSII compared with MDI on glycaemic control was similar to the previous findings of trials using human regular insulin, with the difference in HbA_{1c} concentrations between CSII and MDI being -0.35%. Also, the relative benefit of CSII over MDI was found to increase with higher baseline HbA_{1c} levels (Fig. 1) [20]. In addition,

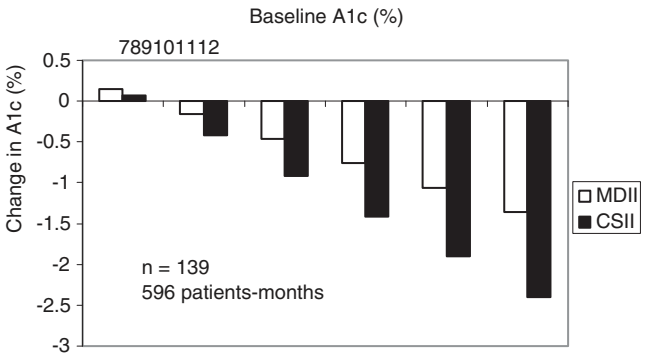

Fig 1. Predicted relative benefits of CSII over MDI in lowering HbA_{1c} according to baseline HbA_{1c} (adapted from [20]).

Table 1
Superiority of short-acting insulin analogues over human insulin in continuous subcutaneous insulin infusion (CSII) treatments.

Authors [reference]	Study design	Patients (n) and type of insulin	Difference in HbA_{1c}
Zinman et al., 1997 [13]	Double-blind crossover	30 CSII with lispro/Humulin	-0.34%
Melki et al., 1998 [14]	Open crossover	39 CSII with lispro/Actrapid	-0.53%
Renner et al., 1999 [15]	Open crossover	113 CSII with lispro/Humulin	-0.13%

the results obtained with CSII were superior to those achieved with MDI whatever the level of baseline HbA_{1c}.

2.2. Hypoglycaemia

As the definition and reporting of hypoglycaemia are different in different trials, it is not easy to make any direct comparisons. However, based on the available data, it appears that CSII use was associated with a decrease in the frequency of mild hypoglycaemic episodes [10], and this was probably related to the lower variability of blood glucose concentrations, as measured by the standard deviation (SD) [9]. In patients prone to severe hypoglycaemia, the use of CSII resulted in a large and sustained reduction in such episodes [21]. In addition, a meta-analysis of randomized controlled trials and observational studies, conducted with CSII and short-acting insulin analogues in patients with severe hypoglycaemia at baseline, showed that severe hypoglycaemia was reduced by a mean of about 75% by CSII treatment compared with MDI in adults as well as in children [22].

2.3. Blood glucose variability

In patients failing to obtain good glycaemic control with MDI, high glycaemic variability was frequently associated with both high HbA_{1c} levels and frequent hypoglycaemic episodes, thus preventing tight insulin adjustments because of the difficulty of predicting blood glucose fluctuations and the fear of having even more frequent hypoglycaemia. The improvement in control achieved by CSII appears to be related to both HbA_{1c} and blood glucose variability with MDI. Indeed, pump therapy was most effective in those least controlled with MDI [23]. CSII reduced both the within-day and day-to-day variability, as determined by the mean amplitude of glycaemic excursions (MAGE) [24], and the SD of mean blood glucose [14,17], probably thanks to better predictability and reproducibility of insulin absorption.

3. CSII *vs* long-acting analogues

Reported improvements in glucose control with MDI using only analogues raised the question of whether CSII was truly an unchallenged "gold-standard" treatment. Therefore, comparison of CSII and MDI using both rapid- and long-acting insulin analogues is clearly of great interest, although few randomized controlled studies have assessed the issue (Table 3).

The first randomized study performed in adults showed similar glucose improvements with the two options [25]. However, it should be noted that the baseline HbA_{1c} in the study was not excessively high (7.7% for CSII and 7.8%

Table 2
Superiority of continuous subcutaneous insulin infusion (CSII) using short-acting insulin analogues over multiple daily insulin injections (MDI) using short-acting insulin analogues.

Authors [reference]	Study design	Patients (n)	Difference in HbA_{1c}	Hypoglycaemic episodes
Hanaire-Broutin et al., 2000 [12]	Crossover	41 MDI/CSII	-0.35%	NS
Tsui et al., 2001 [18]	Parallel	13 CSII 14 MDI	NS	NS
DeVries et al., 2002 [17]	Parallel	39 CSII, 40 MDI	-0.84%	+0.96/patient/week
Retnakaran et al., 2004 [19]	Pooled analysis	139 MDI/CSII	-0.35%	NS

NS: not significant

Table 3
Randomized controlled trials of continuous subcutaneous insulin infusion (CSII) using fast-acting insulin analogues *vs* multiple daily insulin injections (MDI) using fast- and long-acting insulin analogues in type 1 diabetes patients.

Authors [reference]	Study description	Insulin used for MDI	Insulin used for CSII	HbA_{1c} at end of trial
Bolli et al., 2004 [25]	n = 57 (adults), 6 months, randomized	Glargine + lispro	Lispro	CSII: 7.0% MDI: 7.2% (NS)
Hirsch et al., 2005 [27]	n = 100 (adults), 10 weeks, randomized (crossover)	Glargine + lispro	Aspart	CSII: 7.1%* MDI: 7.3% (NS)
Doyle et al., 2004 [26]	n = 32 (children), 16 weeks, randomized	Glargine + aspart	Aspart	CSII: 7.2 MDI: 8.1 (**$P < 0.05$**)

*Significant reduction in fructosamine; NS: not significant.

for MDI). Another study performed in children showed the superiority of CSII on HbA_{1c} levels after 16 weeks [26]. The most recently published short-term randomized crossover study performed in adults comparing CSII and MDI, including glargine, reported lower fructosamine levels and reduced daily glycaemic exposure, as assessed by continuous glucose monitoring, with CSII [27].

Of the three other, non-randomized, studies, the two that were performed in children showed improvements in glucose control only with CSII compared with previous therapy using neutral protamine Hagedorn (NPH) or ultralente insulin [28,29]. The third study, performed in adults, reported significantly lower glucose excursions and glycaemic variability only with CSII [30].

Thus, as CSII may not be superior to MDI using only analogues in all patients, the identification of those patients who are likely to benefit the most from CSII appears to be important. Pickup et al. [31] identified the predictive factors of success in a series of 30 type 1 diabetes patients who were switched from MDI to CSII. The reduction of HbA_{1c} with CSII was related to the level of HbA_{1c} and within-day blood glucose variability at baseline. The patients who may be expected to be the best candidates for CSII are those least controlled with MDI and those particularly exposed to severe hypoglycaemia. CSII remains the only treatment allowing variability of basal insulin delivery to meet anticipated changes in insulin needs. This is particularly important in patients who have variable lifestyle or variable insulin requirements especially at night, including the dawn phenomenon and the problem of recurrent nocturnal hypoglycaemia.

3.1. Quality of life

The assessment of quality of life has been the focus of a limited number of studies, all using different measures and different concepts, thereby making it difficult to draw any definite conclusions. However, these few studies have shown a favourable or neutral effect of CSII therapy on quality of life, depression and anxiety [17,32,33]. An improvement in the quality of life of the parents of children switched to CSII has also been reported [34].

4. Benefits of CSII in type 2 diabetes

CSII is now widely used in type 1 diabetes patients, but its development as a treatment of type 2 diabetes is a much more recent area of research and remains a subject of debate [35, 36]. Type 2 diabetes is associated with insulin resistance and a progressive defect in islet β-cell function. As the defect progresses, the combination of lifestyle changes and oral antidiabetic agents (OADs) fails to maintain long-term optimal diabetes control in most patients, and insulin treatment has then to be implemented. With bedtime insulin injection combined with OADs commonly used as the first insulin regimen, many type 2 diabetes patients eventually require MDI therapy to maintain blood glucose control. However, even if intensive insulin therapy can improve glycaemic control in obese type 2 diabetes patients, it often comes at the cost of high insulin doses that, in turn, may lead to further marked weight gain. In the worst-case scenario, patients gain weight while their glycaemic control remains suboptimal in spite of increasing insulin doses. Also, regimens using short- and long-acting insulin analogues are not superior to human insulin-based regimens in terms of HbA_{1c} and insulin doses required, although they can result in a trend towards less hypoglycaemia and weight gain. For these reasons, it may be useful to consider the potential indications for insulin pump therapy in type 2 diabetes.

4.1. HbA_{1c}

Several authors have reported positive experiences with CSII in small cohorts of severely obese type 2 diabetes patients with poor glycaemic control (HbA_{1c} 10-12%) in spite of intensified insulin therapy using high insulin dosages (1.5-5.0 U/kg) [37,38]. Interestingly, in these particularly insulin-resistant patients, both HbA_{1c} and insulin requirements were decreased with CSII [39].

More recently, four randomized controlled trials compared the potential benefits of CSII *vs* MDI in insulin-requiring type 2 diabetes patients (Table 4). The trial by Raskin et al. [40] compared CSII using aspart insulin with MDI using premeal aspart and one or two injections of isophane as basal insulin. The improvement in HbA_{1c} after 24 weeks was similar in the two groups. In older type 2 diabetes patients (mean age: 66 years), the trial by Herman et al. [41] compared CSII with lispro insulin *vs* MDI with glargine and lispro. HbA_{1c} decreased significantly and similarly in both groups, reaching an optimal level after 1 year. In both these studies, most of the patients were receiving insulin at baseline, but not in an intensified regimen, and HbA_{1c} levels were moderately elevated (8.2%). Thus, it was to be expected that MDI would be more effective than the baseline treatment in these patients. In these populations, therefore, CSII was as effective as, but not superior to, MDI in terms of overall glycaemic control.

Two other studies, each with a crossover design, showed significant improvements in glycaemic control with CSII compared with MDI. The trial by Wainstein et al. [42], conducted in 40 obese type 2 diabetes patients with poor glycaemic control (HbA_{1c} 10.2%), showed the superiority of CSII with lispro insulin *vs* MDI with isophane insulin and human regular insulin in the control of HbA_{1c} levels. The trial by Berthe et al. [43] included 17 patients in poor glycaemic control, treated with two daily injections of premixed insulin (isophane 70/human regular 30), who were allocated to either CSII using lispro insulin or premixed insulin given three times daily. Glycaemic control was improved with both treatments, but to a greater extent with CSII. These two studies indicate the benefits of CSII over MDI; however, the MDI regimens used as comparators were not analogue-based basal-bolus regimens.

Table 4
Studies of continuous subcutaneous insulin infusion (CSII) *vs* multiple daily insulin injections (MDI) in patients with type 2 diabetes.

Authors [reference]	Patients (n)	Diabetes duration (years)	Baseline HbA_{1c}	Type of insulin	OADs	Study description	HbA_{1c}	Insulin doses (U/day)	Hypoglycaemic events	Weight change (kg)	Quality of life
Raskin et al., 2003 [40]	132	12.5	8%	CSII: aspart MDI: 1 or 2 NPH + 3 aspart	No	Parallel-group, 6 months	NS, CSII: 7.6±1.22% MDI: 7.5±1.22%	NS, CSII: 0.7 U/kg MDI: 0.8 U/kg	NS, CSII: 0.8±1.6/month MDI: 1.2±3.1	NS, CSII: +1.7 MDI: +0.9	**Improved** ***P* < 0.001**
Herman et al., 2005 [41]	107	16	8.3%	CSII: lispro MDI: glargine +3 lispro	No	Parallel-group, 12 months	NS, CSII: 6.6±0.8% MDI: 6.4±0.8%	NS CSII: 108±63 MDI: 108±62	NS, CSII: 1.08 MDI: 1.22/week	NS, CSII: +2.1 MDI: +2.6	NS
Wainstein et al., 2005 [42]	40	NA	10.2%	CSII: lispro MDI: 1 NPH +3 human regular	Metformin	Crossover, two periods of 4.5 months	***P* = 0.007**	NS	NS	NA	NA
Berthe et al., 2007 [43]	17	17	9%	CSII: lispro MDI: 3 premixed (lispro–NPH 50/50)	No	Crossover, two periods of 3 months	***P* < 0.03,** CSII: 7.7± 0.8% MDI: 8.6±1.6%	NS CSII: 1 U/kg±0.2 MDI: 1.2 U/kg±0.3	NS	NA	NA

OADs: oral antidiabetic drugs; NPH: neutral protamine Hagedorn; NS: not significant; NA: not applicable

4.2. Hypoglycaemia and weight gain

Three of the four above-mentioned randomized studies showed the superiority of CSII over MDI in terms of glycaemic variability and, in particular, postprandial glycaemic excursions, as assessed by continuous glucose monitoring [43]. In all these studies, mild hypoglycaemic episodes were reported at the same (low) rates with MDI and with CSII. There was no significant difference in the number of patients experiencing either severe hypoglycaemia or the number of severe hypoglycaemic events between MDI and CSII. Insulin dosages increased slightly and similarly with both MDI and CSII in all of the studies, and reached around 1 U/kg. There was also no difference between CSII and MDI in weight gain, which was moderate and in parallel with the improvement in HbA_{1c}.

5. CSII in type 2 diabetes in the long term

All of the above studies were of short duration. Reznik et al. [44] reported the results of a retrospective survey of 102 type 2 diabetes patients using CSII with a median follow-up duration of 24 months. HbA_{1c} improved significantly from 9.3% at baseline to 7.8% after 1 year. Even in the patients who were receiving intensified insulin therapy with a basal-bolus regimen at baseline, the initiation of pump therapy allowed significant improvement in glycaemic control with a 0.9% decrease in HbA_{1c}. Interestingly, a favourable effect was obtained even in patients who were not completely autonomous in managing pump therapy, suggesting that a patient's disability is not limiting if a nurse's assistance is provided for the ongoing management of the CSII device.

In another trial, 59 patients with poor glycaemic control using MDI were switched to CSII and followed for 3 years [45]. The beneficial effects of pump therapy on HbA_{1c} were maintained in the long term (-1.2% after 3 years). Metformin treatment was used with the intensive insulin therapy throughout the study. Most of the excess weight reported was gained during the first year of treatment. These results suggest that routine pump therapy in patients with type 2 diabetes, especially those with chronically inadequate glycaemic control, is both feasible and effective in the long term.

5.1. Quality of life

Several studies in type 2 diabetes report improvement in patients' satisfaction and quality of life with insulin pump therapy. This was particularly well documented in the study by Raskin et al. [40] (Fig. 2). The CSII patients had significantly greater improvement in overall treatment satisfaction: 93% of the pump-treated subjects favoured the pump for reasons of convenience, flexibility, easiness of use and overall preference. In the long-term study by Labrousse-Lhermine et al. [45], quality-of-life assessment showed improvements in both objective and subjective criteria, and in physical and psychological dimensions. Patients using CSII were better satisfied with their treatment and reported a decreased impact of the disease on

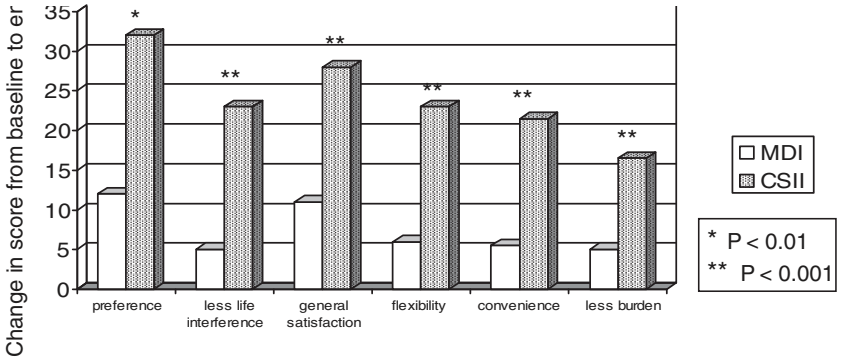

Fig 2. Change-from-baseline improvements in patients' satisfaction subscores with CSII *vs* MDI (adapted from [40]).

their quality of life. At the end of the 3 year study period, 92% of the patients chose to continue with the pump therapy, thus confirming the good tolerability of the pump and the improved quality of life in the long term in patients with type 2 diabetes.

For these reasons, in type 2 diabetes, pump therapy may be a valuable tool, especially for those patients with chronically inadequate glycaemic control, obesity and high insulin requirements despite an intensified and accurately adjusted MDI regimen.

6. Insulin pump treatment: do we need more?

6.1. Pump and catheter features

Today's insulin pumps are highly reliable and easy to use in daily life, at least as regards their basic functions. They have become smaller and more discreet but, also, in some ways, more complex, as many new technological features are now embedded in the pumps, including the different ways of infusing boluses, different patterns of basal rates for different days and reminders for boluses. Bolus calculators are particularly useful for helping patients to adjust their prandial doses. The capability to download data already exists, and may well be accompanied by automatic analysis of these data and by expert advice for treatment adjustment.

However, whereas catheters have considerably improved over the past few years, the technical aspects of pump and catheter handling remain an obstacle for some patients. Filling the pump reservoir, priming the catheter and inserting the needle require precision, skill and time; however, patch pumps should bring about important improvements in this field. Also, avoidance of the catheter and automatic needle insertion/retraction are attractive features that should reduce the discomfort of pump therapy for activities such as showering, sports participation and swimming.

6.2. Insulin

The use of short-acting insulin analogues has considerably improved the day-to-day management of diabetes, particularly in patients using CSII. However, the subcutaneous site introduces delays in insulin kinetics, with the onset of insulin action still too slow and the duration of action still too long to mimick physiological postprandial insulin secretion. Nevertheless, attempts are being made to improve insulin kinetics either by modifying its formulation to reduce the time between insulin injection and its onset of action or by introducing other compounds, such as hyaluronidase, to accelerate the onset on insulin action and reduce its duration.

6.3. Sensor-augmented pumps

Pumps that display continuous glucose monitoring are already available (for example, the Medtronic Paradigm® Veo and the Animas® Vibe). Indeed, not only the actual glucose level, but also the alarms and trends displays can all help the patient to modify his insulin doses. These pumps may also be expected to adapt their calculators to the individual needs of the patient and to not only give advice in real time, but also on the basis of several days'worth of glucose profiles. Such improvements are the next steps towards a closed-loop insulin delivery system.

7. Conclusion

Despite the remarkable improvements in diabetes management thanks to the introduction of insulin analogues, a significant number of patients still cannot achieve their target HbA_{1c} levels without experiencing disabling or severe hypoglycaemia. In such patients, pump therapy provides convenient and flexible insulin delivery while improving their glycaemic control and stability, and quality of life. In addition, efforts are being made to further improve insulin kinetics, and to develop user-friendly monitors and miniaturized insulin pumps. Appropriate teaching and training programmes are necessary, however, to achieve all of the benefits afforded by these technical improvements. Furthermore, considerable work is now in progress to develop algorithms for the automated regulation of glycaemia.

Conflicts of interest statement

H. Hanaire has participated on the boards and in conferences for Medtronic, Eli Lilly, Novo Nordisk and Sanofi-Aventis.

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Improving diabetes management with electronic medical records

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Abstract

Most primary-care physicians have adopted electronic medical records (EMRs) for the management of patients in ambulatory care. Observational trials suggest that the use of EMRs improves the achievement of the recommended standards of diabetes care and intermediate outcomes. A French group of general practitioners has shown, in a randomized controlled trial of diabetes care, the beneficial effects of a follow-up module integrated into an EMR. Electronic reminders, eHealth technology and e-mail messaging to patients integrated into the EMR have also been reported to have a beneficial effect on diabetes care. Some recommendations have been devised for the meaningful use of EMRs to improve the process and, possibly, intermediate outcomes of diabetes care as well. Another potential benefit to consider is the extraction and aggregation of data to create diabetes registers. Large regional and national diabetes registers have been set up in the US and Europe for various purposes, including patient recall, description of care patterns and outcomes, improvement of practices, drug safety, observational research and retrospective trials. In France, the government initiative towards an Internet-based personal health record (PHR) provides an appropriate framework for implementing and sharing the information needed to improve diabetes care, such as electronic summaries of health information, personalized health plans (PHPs), and standardized and structured hospital-discharge forms. All of these materials can be generated from EMRs. The widespread and optimalized use of EMRs for diabetes care with links to the national diabetes register and the capacity to supply PHRs are major considerations. Achieving these goals requires a common initiative comprising primary-care and diabetes scientific societies in cooperation with diabetes patients'associations.

Keywords: *Electronic medical record; Electronic reminders; eHealth technology; Diabetes register; Personal health record; Personalized health plan; Review*

Résumé

Améliorer la prise en charge du diabète à l'aide du dossier médical électronique

La grande majorité des professionnels de santé exerçant en ambulatoire utilisent un dossier informatisé pour gérer la prise en charge de leurs patients. Plusieurs études observationnelles suggèrent que l'utilisation de ces dossiers améliore la prise en charge des patients diabétiques et les résultats intermédiaires de cette prise en charge. Une étude française contrôlée en soins primaires a montré que l'utilisation d'un tableau de bord de suivi intégré au logiciel médical améliorait les procédures de suivi des diabétiques. L'association de rappels électroniques et de certaines fonctionnalités Internet, dont l'envoi d'e-mail sécurisés aux patients, parait également améliorer cette prise en charge. Sur ces bases, des recommandations pour l'utilisation optimale de ces logiciels peuvent être formulées. Une autre potentialité de ces dossiers médicaux est de favoriser la constitution de registres informatisés par extraction automatisée de données: de grands registres régionaux et nationaux de diabétologie ont été établis aux États-Unis et en Europe, avec des fonctions de rappel des patients, d'évaluation et d'amélioration des pratiques de pharmaco-vigilance. Ces registres sont également utilisés pour réaliser des études observationnelles rétrospectives à grande échelle. En France la mise en place du Dossier Médical Personnel (DMP) pourrait être une opportunité de mettre à la disposition sécurisée des professionnels et des patients diabétiques des informations utiles à la prise en charge, tel un résumé médical de synthèse, des Plans Personnalisés de Santé et des compte-rendu hospitaliers structurés et standardisés. Tous ces éléments peuvent être issus d'un dossier médical informatisé. L'utilisation large et optimisée du dossier médical informatisé pour la prise en charge des diabétiques, en lien avec un registre national du diabète et approvisionnant le Dossier Médical Personnel sont des enjeux majeurs. Leur atteinte nécessite une initiative des sociétés savantes de diabétologie et de médecine générale, en lien avec les associations de patients diabétiques.

Mots clés : Dossier médical informatisé ; Rappels informatiques ; Technologie Internet ; Registre du diabète ; Dossier Médical Personnel ; Plan personnalisé de santé ; Revue générale

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1. Introduction

Health information technology is assumed to enable providers to improve quality of care and target interventions to patients, especially those with chronic conditions. For this reason, the use of electronic medical records (EMRs) has been encouraged in the management of diabetic patients according to the Saint-Vincent Declaration for quality assurance in diabetes in 1991. Since then, the widespread use of EMRs for the follow-up of patients has become a fact in all developed countries.

The present development and future perspectives of EMRs can be considered from several points of view: the provider's point of view whereby such records are used daily at various points in the care and management of patients; the public healthcare point of view in which a concrete expression of their value is the national or regional registers established in several countries; and the patient's point of view in which the current issue is the shared use of medical data by different health professionals.

2. Utilization of EMRs at the point of care

In France, hospital diabetes departments introduced electronic diabetes databases for inpatients as early as in 1985 [1]. Their goals were to structure the clinical management of diabetic patients, improve communication with general practitioners and promote regular quality-assurance processes. While hospitals with automated notes, records, order entry and clinical-decision support systems probably have fewer complications and lower costs [2], the true impact of these EMRs in French hospitals has not been evaluated.

In fact, most primary-care physicians have adopted EMRs for the management of patients in ambulatory care, which has made it possible to record patients' demographics, histories, details of recent care and up-to-date problems, and active medication lists, as well as to prescribe medications. These functions have important implications for the management of chronic diseases such as diabetes. Indeed, several randomized trials of evidence-based electronic reminders integrated into EMRs have reported beneficial effects compared with the usual care, with increasing rates of recommended care for diabetes [3], but the impact of individual reminders is variable. Reminders for annual cholesterol examinations, antiplatelet use and foot examinations have generally been reported to have significant positive effects [4,5], and electronic reminders are simple procedures to use. However, one caveat is that their efficiency appears to be less important than performance feedback and also appears to deteriorate with time [6].

Using a more global approach, a French group of 50 general practitioners recruited 2715 diabetic patients into a randomized controlled trial to test the effects of a follow-up module implemented through EMRs *vs* follow-up with only EMRs. The module was based on guidelines and generated an alarm if the recommended procedures were not recorded by the planned date. The adjusted difference between groups was statistically significant for recording body mass index (BMI), foot and fundus examinations, and electrocardiography, whereas there were no differences in HbA_{1c}, lipid and microalbuminuria tests [7]. Other groups of physicians working in 'multidisciplinary practices' have adopted similar approaches to improve the quality and safety of diabetes care, including allowing access of all members of the care team (physicians, nurses, pharmacists) to EMRs [8]. Also, instead of using follow-up modules dedicated to a given disease, some teams have preferred to define and implement only key items in the EMR that have been selected according to the patient's disease.

EMRs can incorporate a variety of decision-support facilities related to eHealth technologies, such as electronically returning the results of laboratory tests, archiving radiological reports and referrals, and accessing expert systems. E-mail messaging to patients also appears to be a meaningful use of the EMR: in a study of 35,423 patients with diabetes, hypertension or both, the use of secure patient-physician e-mails over a 2 month period was associated with a statistically significant improvement in effectiveness of care [9]. In addition, there is growing interest in giving patients a direct link to their EMRs *via* the Internet. One randomized controlled study of 244 patients allowed the pre-visit use of online personal health records (PHRs) linked to EMRs, enabling patients to author a "diabetes care plan" for electronic submission to their physician: although the intervention increased rates of diabetes-related medication adjustments, low rates of online patients' registration limited the intervention's impact on overall risk-factor control [10]. However, a review found little evidence that eHealth technologies integrated within EMRs had any positive impact on the quality and safety of care [11].

An observational study of 22,207 patients with diabetes compared clinical practices using EMRs with those using paper-based records, and examined the independent association of EMR use with achievement of quality standards of care. After adjusting for covariables, the achievement of composite standards for diabetes care was 35.1% higher at EMR *vs* paper-based sites ($P<0.001$), while the achievement of composite standards for intermediate outcomes [HbA_{1c}<8%, blood pressure (BP) <140/80 mmHg, low-density lipoprotein (LDL) cholesterol <100 mg/dL or statin use, BMI<30 kg/m^2, non-smoker] was 15.2% higher ($P = 0.005$) [12].

Although resistance to change negatively affects physicians' adoption of EMRs, there is widespread professional agreement over their use [13]. The main factors that influence the acceptance of EMR use by physicians are their user-friendliness, demonstrability of results, system compatibility with the practice and benefits for everyday practices [14].

To summarize, some recommendations can be drawn for the meaningful use of EMRs to improve the process and possibly the intermediate outcomes of diabetes care as well (Table 1). Another potential benefit to consider is the extraction and aggregation of data from EMRs to build diabetes registers.

Table 1
Activities that contribute to the meaningful use of electronic medical records (EMRs) in diabetes care.

Recording patient demographic data, vital signs and medical history
Maintaining active medication list and active medication allergy list
Prescribing medication using a medical dictionary
Recording smoking status
Recording diabetes status and complications
Maintaining an up-to-date list of current problems
Incorporating laboratory test results as structured data
Implementing and using electronic reminders
Generating lists of patients to include in medical interventions, education or research
Generating forms for patient recall and follow-up care
Generating forms for other professional communications and information
Providing patients with electronic access to their health information
Implementing indicators for clinical-practice improvements
Reporting clinical quality measures to insurance companies
Exporting data to diabetes registers

3. Implementation of national and regional registers

Earlier registers served as central registers based on structured datasets completed on paper forms and laboratory reports. Examples of such registers are DREAM and DIALOG, which were established at a district level to establish the structured recall of patients [15], and to prompt an annual review of diabetes across both primary and secondary care [16]. Increases in the proportion of patients achieving the recommended processes of care and intermediate-outcome treatment targets were reported [17], but these benefits were achieved at the cost of having to make requests of specific staff members to enter these data, a cost that has limited the use of the data over time.

As a consequence, these registers evolved into electronic data exchanges involving EMRs and other databases, a transition that made it easier to identify benchmarks [18]: the first step involved describing the clinical practices and their temporal trends in large groups of patients, then evaluating the differences between recommendations and everyday practices and, finally, improving the quality of patients' management. Some registers address specific topics: the Finnish Registry includes patients who underwent coronary revascularization. On comparing the pathways of diabetic patients leading to surgery between 1998 and 2007 with the pathways of patients without diabetes, it was found that fewer operations were performed during the first coronary heart disease (CHD) hospitalization of diabetic patients, and that they also experienced more emergency hospital admissions [19].

More recent datasets, such as the Swedish [20] and Danish [21] Diabetes National Registers, aim to gather data from all diabetic patients across the nation on a yearly basis. Data are collected from actual patients' visits to primary healthcare and from those who attend hospital outpatients clinics. The Swedish register (1996–2011) includes 24 variables and covers up to 70% of the population with diabetes. The Veterans Health Administration (VHA) has developed a sophisticated electronic system of medical records combined with a quality measurement approach for the management of common chronic conditions. It has been suggested that this system is behind the better management of diabetic patients observed in the VHA compared with a nationwide sample of patients with diabetes [22]. Beginning in the early 1990s, Kaiser Permanente, the largest managed-care organization in the US, established the HealthConnect EMR platform, which has more than 8.6 million users, including physicians, nurses and pharmacists [23]; this was followed, in many community-health centres, by the development of shared and integrated EMR systems [24]. In the UK, a large national database of routine general practices, the General Practice Research Database (GPRD), was established in 1987 and contains data derived from the computerized records of around five million patients [25].

Besides their value for quality control and benchmarking, these databases have other potential functions (Table 2). For observational research in primary-care settings, cohorts including thousands of patients can be generated retrospectively and followed for 4 to 5 years. If necessary, data can be linked with other information issuing from insurance-company claims and hospital-discharge registers. Based on these databases, an increasing number of retrospective observational trials have been published in recent years. The question of the true value of these trials is still pending, however, because they are known to be subject to bias and confounding factors, and to have a potential for high rates of patients lost to follow-up. On the other hand, the sampled populations are representative of those seen in routine clinical practice, and clearly reflect the outcomes of treatments and management in "real-world" healthcare. Nevertheless, their results must be interpreted with caution and with respect to the characteristics of the selected populations.

In France, the implementation of these registers has been limited to a few localized experiences, such as diabetic patients treated with insulin pumps [32]. A few private databases have been supplied by volunteer primary-care physicians remunerated by free use of the EMRs, but they still provide only partial data on the management of patients and do not easily allow researchers to perform longitudinal trials. The ENTRED (*Echantillon National Témoin Représentatif des Personnes Diabétiques*; Representative National Sample of the Diabetic Population) study, which described the management of representative samples of diabetic patients in 2003 and 2007,

Table 2
Potential functions of diabetes registers.

Improving clinical practice by prompting annual reviews and identifying benchmarks
Patient recalls
Measuring care patterns and health outcomes [26, 27]
Clinical epidemiology
Drug safety [28]
Pharmacoeconomics
Developing new models of primary-care delivery [25]
Observational research and retrospective trials [29, 30]
Planning health services and public-health initiatives [31]

relied mainly on French national health insurance claims, which has some limitations related to the estimation of outcomes and the effects of non-reimbursed medical procedures such as foot examinations [33]. In this case, it is likely that a link with a national register based on automatic extractions from EMRs would have improved the study's results. In addition, it has been shown in the US that relying on insurance claims rather than on EMRs has the potential to underestimate the quality of care, particularly as regards cholesterol screening, influenza vaccination, nephropathy screening and HbA_{1c} testing [34]; such underestimation is also likely to arise in France because many diabetic patients have a follow-up in public hospitals with no detailed reports of insurance claims.

All these facts suggest that creating the conditions allowing a National Diabetes Register to be set up in France is of primary importance. The first condition would be to ensure the gathering of data through simple electronic extraction from both primary- and secondary-care EMRs. The second condition would be to promote agreement concerning a scientific standard reference for assessing follow-ups and treatment performance; the annual review designed and tested by diabetes networks could provide the basis for such a consensus [35]. The third condition would be to determine which functions should be a priority for this register, as that would be a determining factor for the type of financial support needed.

4. Secure transmission and shared use of medical data: the PHR system

In France, the government initiative toward an Internet PHR system provides the appropriate framework for implementing and sharing the information needed to improve diabetes care. The objective of the PHR is to gather together all medical information to help in the management of patients and coordination of their care, and to provide secure access to this information. A central goal of the online PHR system is to provide patients with access to their health information to improve their interactions with healthcare professionals.

Towards these ends, structured documents can be stored in the PHR. Some of these documents can be generated from the EMR, with one of the most important of these being an electronic form of health information that summarizes the patient's medical history, medication list, medication allergies, and all current and active diagnoses. This form should be made available to patients, physicians and hospital teams.

Another important stored document is the patient's personalized health plan (PHP), which can be regularly updated by the general practitioner to deal with the patient's current problems, with or without the help of a health network. The plan includes any scheduled medical, educational and social interventions, the names of the persons responsible for these interventions and the scheduled deadline for their implementation. The PHP can be sent to patients and healthcare professionals *via* secure e-mail messages. Standardized and structured hospital-discharge forms and instructions can also be sent to general practitioners through secure e-mails.

5. Conclusion

The modern application of information technology to medical records has the potential to improve the quality, safety and outcomes of diabetes care. The cornerstone of these improvements is the widespread use of EMRs in primary care, with appropriate features for the management of chronic diseases. These EMRs could also be linked to a national register to supply Internet-based PHRs with key information. Achieving these goals will require a common initiative among primary-care and diabetes scientific societies in cooperation with diabetes patients' associations.

Conflicts of interest statement

The author has no conflict of interest to disclose regarding the subject of this paper.

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Improving diabetes management with electronic health records and patients' health records

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Abstract

The lack of patient engagement and clinical inertia both contribute to suboptimal diabetes care. However, both obstacles are amenable to informatics- and Internet-based interventions.

The use of electronic medical records (EMRs) is now established as being useful for improving diabetes care. Intelligent records that integrate computerized decision-support systems are now able to recommend care protocols tailored to risk levels. Web-based personal health record (PHR) systems, shared with healthcare providers, could also provide added value by promoting self-management of the behaviours related to diabetes. These Web-based programmes include patients' access to EMRs, uploading of glucose monitoring results, a glucose diary, secure e-mail with providers, manual or automated feedback on blood glucose readings and other risk factors, an educational website, and an online diary for entering personal information on exercise, diet and medication. The integration of Web-based patients' systems into the EMR used by physicians is the next frontier. In addition, the input from "smartphones" that are able to provide real-time support to patients could contribute to the reorganization of diabetes care.

Convincing data on HbA_{1c} improvements with such systems are available for type 2 diabetes, but are still equivocal for type 1 diabetes. Obstacles include patients' compliance with the technology, their ergonomic design and the need to reimburse providers for their care. Designing appropriate electronic tools and tailoring them to the conditions in France merits our attention.

Keywords: *Diabetes care; Electronic health record; Patient health record; Internet; Web; Telemedicine; Review*

Résumé

Améliorer la prise en charge du diabète à l'aide du dossier médical électronique et du dossier de santé tenu par le patient

Le défaut d'investissement du patient et l'inertie clinique contribuent à une prise en charge insuffisante du diabète. Ces deux obstacles pourraient être levés par une intervention basée sur les outils informatiques et Internet.

Il est maintenant établi que l'utilisation d'un dossier médical informatisé améliore la prise en charge du diabète. Des dossiers intelligents, intégrant des systèmes automatisés d'aide à la décision, sont capables de recommander des protocoles de soin ajustés sur le profil de risque du patient. Par ailleurs, des dossiers de santé personnels pour le patient sont apparus qui, lorsqu'ils sont partagés avec le soignant, ont une valeur ajoutée en favorisant l'autoprise en charge des comportements inhérents au diabète. Ces programmes accessibles sur le Web fournissent plusieurs fonctions: dossier médical, téléchargement des glycémies capillaires, tenue d'un carnet glycémique, messagerie sécurisée en lien avec le soignant, feedback manuel ou automatique sur les glycémies, site Web éducatif, journal en ligne (exercice, alimentation, médicaments). L'intégration du dossier de santé patient et du dossier médical informatisé médecin est la prochaine étape. Enfin l'intégration de smartphones pouvant fournir une aide en temps réel pourrait contribuer à réorganiser les soins du diabète.

Des données convaincantes sur l'HbA_{1c} sont disponibles avec ces outils pour le diabète de type 2, elles sont encore équivoques pour le diabète de type 1. Les obstacles sont l'adhésion du patient à la technologie, l'ergonomie à parfaire, et la rétribution financière des soignants. La mise au point de tels outils adaptés au contexte français devrait être considérée avec attention.

Mots clés : Gestion du diabète ; Dossier médical informatisé ; Dossier de santé du patient ; Internet ; Web ; Télémédecine ; Revue générale

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1. Introduction

Despite the availability of international guidelines and major efforts towards improvements, the care of diabetic patients remains suboptimal. Two important barriers are the lack of patients' engagement with therapeutic care plans (related to insufficient knowledge, motivation and decision-support help) and the lack of medication adjustment by physicians (related to clinical inertia) during clinical encounters. Both obstacles are believed to be amenable to informatics-based interventions and, especially, Internet-based strategies.

2. Electronic record-based clinical decision-support systems

From the physicians' point of view, efforts have been made to allow electronic medical record (EMR) systems to provide adequate decision-making support for patients' management. A recent survey conducted among 46 practices, involving 27,207 diabetic patients, established that the use of an electronic health record was associated with improved diabetes care compared with sites using paper records [1]. However, an appropriate computerized database cannot rely solely on basic features such as the collecting, managing and analyzing of information, and graphic representations of data. Instead, several reports have demonstrated that computerized decision-support systems integrated within the EMR can improve prescribing and quality of care. Indeed, some available systems can even provide patient-specific summaries and recommendations. The Joint Asia Diabetes Evaluation (JADE) Program is a Web-based programme incorporating a comprehensive risk engine, care protocols, and clinical-decision and self-management support to improve ambulatory diabetes care. Its risk engine predicts the 5 year probability of major clinical events based on parameters collected during annual assessments. Using risk stratification, the e-portal recommends a care protocol tailored to risk levels with decision support triggered by various risk factors. This e-portal also displays trends of risk-factor control at each visit to promote doctor-patient dialogues to empower both parties to make informed decisions [2].

3. Web-based shared systems for diabetes self-management

From the patients' point of view, Web-based personal health record (PHR) systems, shared with healthcare providers, have been advocated as a means of improving diabetes care. A growing subset of PHRs has also opened up the possibility of engaging patients in their own care by promoting self-management of the complex behaviours related to their diabetes, such as glucose monitoring, insulin and other medication management, psychotherapy and social support, physical activity promotion and nutrition counselling.

The first such PHR systems introduced were Internet-based glucose monitoring systems (IBGMS). A Korean test conducted in patients with type 2 diabetes (T2D) demonstrated that the IBGMS, which provided frequent and responsive interactions between patients and their physicians online, was more effective than face-to-face diabetes follow-ups [3]. Long-term follow-up (30 months) also showed that IBGMS were superior to conventional care on HbA_{1c} outcomes [4]. In addition, in a similar study, 104 T2D patients received a notebook computer, glucose and blood pressure monitoring devices, and access to a care management website. The website provided educational modules, accepted uploads from monitoring devices and had an internal messaging system for patients to communicate with their care manager. Significant improvements in HbA_{1c}, blood pressure and lipid values were observed in the Web-based group over 12 months, with a correlation between a greater number of website data uploads and a greater decline in HbA_{1c} [5].

There is now growing interest in the use of Web-based systems that allow patient-initiated glucometer uploads to facilitate treatment intensification by providers. The rationale for PHR development relies on the four key domains in Wagner's chronic care model: self-management support for patients; delivery system design; clinical information systems; and clinical decision support. In patients who desire an active role in managing their own health and a collaborative relationship with their healthcare providers, this technology enables self-management support with online real-time delivery of automated, yet tailored, messages. Patients can access their information, input their data and receive support 24 h a day, as modern PHR systems are fitted with a virtual "coach" to provide individualized guidance and support according to available analyses and the patient's characteristics. Empowering patients with essential information, online help in decision-making and communication support from their healthcare provider constitute the main rationale of these systems.

The main features of these Web-based programmes include patients' access to EMRs, uploading of glucose monitoring results, a glucose diary, secure e-mail with providers, manual or automated feedback on blood glucose readings and other risk factors, an educational website, and an online diary for entering information on exercise, diet and medication.

Indeed, one of the first of such PHR approaches raised some interesting findings. Patients were enrolled in a diabetes care module that included access to their EMRs, secure e-mail with healthcare providers, ability to upload blood glucose readings, feedback on glucose readings, an educational website with endorsed content, and an interactive online diary for entering exercise, diet and medication. From a qualitative analysis of this pilot trial, six themes emerged: feeling that non-acute concerns are uniquely valued; enhanced sense of security regarding health and healthcare; frustration with unmet expectations; feeling more able to manage; valuing feedback; and difficulty fitting the programme into activities of daily life [6].

This Web-based programme was tested later in Seattle, WA, in a 12 month randomized trial of 83 T2D patients with baseline $HbA_{1c} \geq 7\%$. This trial showed a 0.7% benefit in HbA_{1c} levels in the Web group [7]. Interestingly, however, a similar trial run by the same team involving 77 type 1 diabetes (T1D) patients with baseline HbA_{1c} at 8% failed to demonstrate the superiority of Web follow-up [8].

Nevertheless, two other similar Web-based diabetes management applications (MyCareTeam and ALR Technologies) were tested in Boston, MA, and Vancouver, Canada, in T2D patients, and showed significant improvements in HbA_{1c} [9,10]. The latter system allows data to be presented in table and graph formats according to the time of day, and automatic calculations are done to show the average, standard deviation and range for the specific time period. The ALR system also allows the patient to input medications, set alarms, view a summary of readings and send messages to the endocrinologist, who then views the readings and sends the patient back some comments or recommendations. The endocrinologist's feedback may include changes to insulin dosage, suggestions on testing frequency and compliments on the patient's behaviour [10]. It is worth noting that patient– healthcare provider interactions and, in particular, those that are more personalized will increase the patient's frequency of blood glucose monitoring [11].

At present, the trend is for PHR systems to extend their features beyond glucose-monitoring data management, and other clinical and biological data collection, to take full advantage of the technology in the field of education reinforcement. In the more recent systems, called "patient-oriented education management systems", or POEMs, the patient's educational materials, medication data and laboratory test results are reorganized in such a way that information is easily accessed on the Web by the patient or his relatives. These systems can provide reminders for the next face-to-face follow-up with e-mails and short messages *via* a cell phone. A randomized trial of 274 T2D patients with an 8 month follow-up showed that users of such a system had significant improvements in HbA_{1c} and lipid values, with an average number of system log-ins of 8 per month [12].

When patients who were users of such Web portals were asked to rate the features they favoured the most, the top-ranking features were the online calculator for estimating blood glucose control (characterized as "very useful" by 74% of patients), appointment reminder systems (74%), e-mail access to the healthcare team (74%), personal tracking logs (69%) and online scheduling (69%) [13].

Most of the studies of diabetes patients' health-record systems have been carried out in North America. However, a multicentre trial (TELEDIAB-3) testing a Web-based portal (MEOS) and allowing T1D patients to download glucose monitoring data, HbA_{1c} results, secure e-mail access to the diabetes team, prescription renewal, and warning thresholds for glucose and HbA_{1c}, is currently ongoing in France.

4. Integration of patients' electronic health and healthcare records

The coexistence of two electronic information systems, one managed by the patient and the other by the healthcare provider, raises several practical issues. Few Web-based patients' systems are linked directly to the EMRs used by physicians. The integration of both records into what some call the "patient Web portal" (PWP) has been associated with better patient outcomes in some reports. In one study, a diabetes-specific PHR that imports clinical and medication data, provides patient-tailored decision support and enables the patient to author a "diabetes care plan" for electronic submission to his physician prior to any upcoming appointments, was linked directly to the EMR system of a large academic medical centre (Partners HealthCare System, Boston, MA) *via* secure Internet access. This PWP, dubbed "Patient Gateway", allows patients to interact directly with their EMR. In fact, a specific diabetes interface was designed to maximize patients' engagement by importing their current clinical data in an educational format [14].

Other similar systems have also been reported. In one, at each patient visit, the system automatically downloads the patient's medical services record, prescriptions, laboratory test results and patient educational materials, and organizes them into a series of case folders based on the patient's medical service history in hospital. The system can also send patients reminders of when to return to hospital for further treatment under specified conditions, such as 1 week before an appointment or during the period of their HbA_{1c} test if it is more than 3 months away, and make emergency calls if an anomaly in a laboratory result is found [15]. The University of Pittsburgh's HealthTrak, based in the physician's office, connects the patient, physician and EMR, and provides secure electronic communication with the physician's office, along with preventative healthcare reminders and disease-specific tools and information, as well as remote access to laboratory test results [16].

5. Conclusion

Electronic health-record technology using Internet-based strategies is believed to improve diabetes patient outcomes through enhanced education and patient support, and through reduced clinical inertia on the part of the healthcare provider. So far, however, no HbA_{1c} improvement with such an approach has been reported in large series of T1D patients. It appears that such improvement is more likely to occur in T2D patients. Major obstacles to the wider implementation of these technologies include patients' computer skills, compliance with the technology, their structural and technical design, and the need to reimburse providers for their care. However, integration of the records of both patients and healthcare providers, as well as the input of mobile smartphone tools, such as providing real-time support to patients, may bring a new paradigm of the way diabetes care is organized and

delivered in the near future. The convergence of all these electronic tools involving various healthcare professionals is also likely to be critical for the success of telemedicine in the field of diabetes. Finally, the data appear to be sufficiently convincing to call for the use of both EMRs and PHRs for diabetes care in France.

Conflicts of interest statement

The author declares having perceived some fees from Sanofi for his participation to a scientific board dedicated to new technologies and telemedicine.

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How technology has changed diabetes management and what it has failed to achieve

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Abstract

Tremendous improvements have modified diabetes management from pure clinical diagnosis and the discovery of insulin to continuous subcutaneous insulin infusion (CSII) coupled with continuous glucose monitoring (CGM) to allow patients to adapt insulin delivery to glycaemia on a virtually "real-time" basis. Insulin was first discovered in 1923 and, in less than a century, it has been purified, humanized and now synthesized by genetically modified microorganisms. Insulin analogue, kinetics and reproducibility now allow near-normal glycaemia to be targeted without increasing hypoglycaemia, thus allowing greater flexibility in the patient's day-to-day life. In addition, advances have been made over the past few decades in the development of the necessary and complementary technologies for insulin infusion, glucose measurement, glucose insulin interaction and telemedicine. The major remaining limitations are the lack of glycaemic regulation on insulin administration and the burden of parenteral delivery. Thus, the dream of both patients and diabetologists is to close the loop and to build an artificial pancreas.

Keywords: *Type 1 diabetes; Diabetes technology evolution; Continuous insulin infusion; Continuous glucose monitoring; Sensors; Review*

Résumé

En quoi la technologie a-t-elle changé l'approche du diabétologue ? En quoi ne l'a-t-elle pas fait ?

D'importants progrès ont transformé la prise en charge du diabète, du diagnostic clinique, de la découverte de l'insuline à la perfusion continue d'insuline couplée à la mesure continue du glucose ; techniques qui permettent au patient d'adapter l'administration de l'insuline à la glycémie en temps réel. L'insuline a été découverte en 1923. En moins d'un siècle, elle a été purifiée, humanisée puis synthétisée par génie génétique. Les analogues, de par leur pharmacocinétique et leur reproductibilité, permettent de tendre vers des glycémies les plus normales possibles sans augmenter le risque d'hypoglycémie, ils donnent une plus grande flexibilité au diabétique dans sa vie de tous les jours. Des progrès considérables ont été faits dans le domaine de l'administration de l'insuline, de la mesure de la glycémie et de la télémédecine. La principale limite à la prise en charge actuelle est l'absence d'administration d'insuline réellement régulée par la glycémie et le poids de l'administration parentérale de l'insuline. Le rêve de tout patient et de tout diabétologue : le pancréas artificiel est encore, pour le moment, hors de portée.

Mots clés : Diabète de type 1 ; Évolution des technologies dans le diabète ; Infusion continue d'insuline ; Mesure continue du glucose ; Capteurs de glucose ; Revue générale

1. Introduction

Diabetes was first described by the Ancient Greek physician Aretaeus of Cappadocia, who first coined the term "diabetes". In Ancient India, diabetes was called "sweet urine disease"; they had observed that ants were attracted to the patients' urine, and this became a positive test for the disease. Later, European physicians would taste urine samples to identify whether or not it had a "sweet" taste.

The big step for physicians in this field was dosing of glucose in venous glycaemia coupled with urine strips. This "security glycosuria" to avoid hypoglycaemia was, at the time, the admitted dogma; it impressed upon diabetic patients the notion of insulin dose adaptation, hypoglycaemia preservation

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and microangiopathic complications. A significant correlation between long-term metabolic control and fewer chronic diabetes complications was shown in the Diabetes Control and Complications Trial (DCCT) [1], which involved modifying diabetes management and aimed for "near-normal glycaemia" coupled with a low frequency of hypoglycaemia. To achieve this goal, new tools were developed.

2. The first technical tool: Urine-testing

The first method for assessing glycaemic status was the urine strip, which measures glucose and ketones; however, results were delayed depending on vesical repletion [2]. Urine was tested regularly to allow adaptation of insulin doses, and glycosuria without ketones was the goal to achieve at bedtime [2]. Ketonuria associated to glycosuria indicates a catabolic state and the breakdown of fat; in this case, the patient was advised to take measures to keep well-hydrated, to take extra insulin and to test again every 2h.

The measurement of ketonaemia was a huge improvement to day-to-day diabetes management, as patients were more compliant with testing blood than urine; ketonaemia is also more reliable, has no delay and responds quickly, thereby immediately demonstrating the efficacy of any therapeutic decisions made. Furthermore, this tool is easier to use as the patient can use the same blood drop to measure ketonaemia. Few glucometers provide this function. The strips are reimbursed in France for type 1 diabetes (T1D) patients for continuous subcutaneous insulin infusion (CSII) and during pregnancy.

3. Self-monitoring of blood glucose: A revolution for patients and physicians

In 1969, the first glucose monitoring device (Ames Reflectance Meter) appeared. It was based on glucose oxidase and assessed glucose levels in a 50 μL blood sample. In the 1970s, self-monitoring of diabetes became available with the creation of the personal glucose monitor (Fig. 1A), which allowed multiple capillary blood glucose tests, insulin dose adaptation and, thus, better glucose control in terms of both hyper- and hypoglycaemia.

Self-monitoring of blood glucose (SMBG) devices were widely introduced in the early 1980s and became commonplace in the 1990s as a replacement for urine testing to allow diabetic patients to assess their current level of glycaemia. Patients were taught how to use these SMBG readings to guide their decisions for immediate treatment. It has been shown to be an essential component in the intensive management of T1D patients.

Compared with the older devices, SMBG instruments are now smaller, with design improvements: most of them no longer require changing codes when switching strip batches (no coding feature), and they now give their results in < 5s from only 0.5 μL of blood. Haematocrit, peritoneal dialysis and blood oxygenation, as well as alternative puncture sites (arm, ear), are also less likely to interfere with the dosage.

Analytical or statistical accuracy of SMBG systems is necessary between reference and SMBG values to prevent the possibility of serious errors in treatment decision-making. The American Diabetes Association (ADA) has suggested

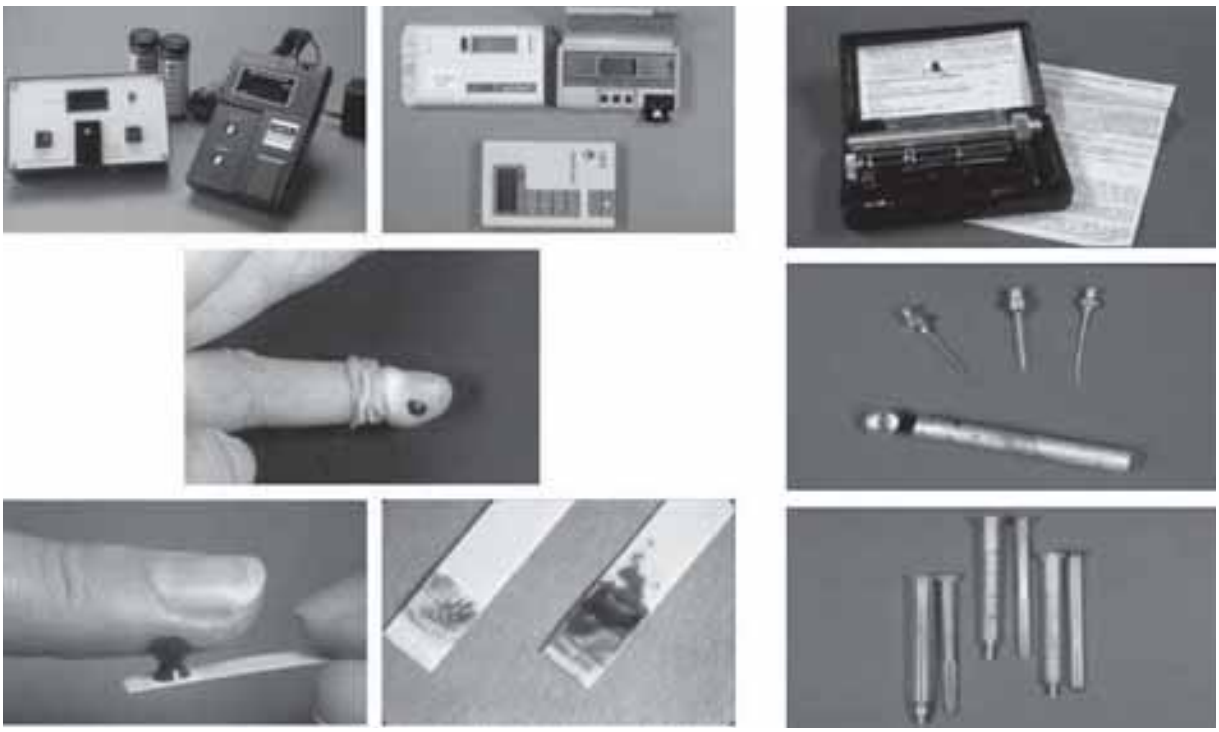

Fig. 1. Improvements in glucose monitoring and insulin syringes: A) the first portable glucose monitors were heavy, required large blood samples and were highly variable in performance; and B) some old-fashioned insulin injection systems

A | B

that systems should achieve an analytical plus user error of < 10% with blood glucose levels between 30 and 400 mg/dL. This means that, for a reference value of 74 mg/dL, an SMBG value would be considered accurate if it were between 59 and 89 mg/dL. However, these two values lead to entirely different clinical responses. The term "accuracy" as applied to analytical performance is defined by the International Organization for Standardization (ISO) as "the difference between the expectation of measurement results and the true value of the measured quantity" – in other words, the assessment of the difference between obtained results (by the blood glucose monitor) and the true value (determined by a reference method that remains undetermined) [3]. Precision and reproducibility may still be improved, and the error grid assessed, in most SMBG devices. Altitude and temperature remain additional sources of error.

Thus, the overall performance of an SMBG system is a combination of the analytical performance of the device, quality of the test strips and performance of the user. Improving the accuracy of glucose monitoring systems emphasizes technical improvements and better patients' education to reduce user errors, such as failure to correctly calibrate the meter, dirty meters, inadequate hand-washing and improper storage of the test strips [4].

Despite these limitations, SMBG is now essential for intensive T1D patients' management to achieve and maintain the tight levels of glucose necessary to avoid macro- and microangiopathy [1]. Virtually all intensive insulin-therapy programmes depend on the measurement of glucose levels at least four times a day to determine the appropriate basal and preprandial doses [5]. The ADA also recommends that patients with T1D monitor their blood glucose at least three times a day [6]. For most patients with T1D, testing blood sugar levels before and at intervals after meals; before, during and after exercise; and occasionally during the night will provide useful information for adjusting insulin and carbohydrate intakes. With "conventional" insulin therapy, oral agents and glucagon-like peptide-1 (GLP-1) analogue regimens, SMBG may be less frequent, but remains mandatory to avoid hypoglycaemia during changes in treatment or lifestyle [5].

However, the efficacy of SMBG in improving glycaemic control in type 2 diabetes (T2D) patients is more controversial. Multiple observational studies have evaluated SMBG in T2D, with some showing benefit [7,8] and others not [9-11]. Meta-analyses of randomized trials report conflicting results, with one reporting no benefit [12], and two subsequent analyses, limited to trials evaluating SMBG in non-insulin users, reporting a modest decrease in HbA_{1c} in the SMBG group compared with the controls (pooled mean difference: -0.24%) [13,14]. In one study of newly diagnosed patients, SMBG was associated with higher scores on a depression scale [15].

To improve diabetes control, monitoring blood glucose also needs to be considered a tool for modifying treatment and behaviour; indeed, it should drive any therapeutic decisions. SMBG provides important information with which motivated educated patients can safely modify their behaviour and improve their HbA_{1c} levels. SMBG means collecting glycaemia and treatment in a logbook, and changing the therapy, food and/or exercise patterns according to glycaemic variations.

As the use of SMBG grows, it has to become cost-effective. In an economic analysis of SMBG alone or with additional training on how to incorporate the results into self-care, SMBG proved unlikely to be cost-effective in addition to the usual standardized care [16]. In France, strip reimbursement has recently been limited to 200/year for patients treated with oral antidiabetic agents (OADs).

At present, the use of computerized glucose monitoring with memory meters is expanding. This allows the analysis of hundreds of data, and the calculation of mean blood glucose levels, daily fluctuations and hypoglycaemia frequency. It is a useful tool for clinical trials, but also for patients' clinical management and education when data are discussed with caregivers.

Nevertheless, one of the main limitations of SMBG is the small amount of data provided: four to six capillary blood glucose values a day are often the best a patient can perform on a routine basis, considering the burden, pain and time involved with the technique. Moreover, glycaemic variations may be missed (Fig. 2), particularly at night-time, thereby leading to wrong therapeutic decisions. One recently developed solution is the continuous glucose monitoring (CGM) system.

4. Continuous glucose monitoring: Identification of undetected glycaemic fluctuations

The first CGM system was approved by the US Food and Drug Administration (FDA) in 1999 and was rather like a "glycaemic Holter" device, with the patient remaining unaware of the glycaemic data until they were downloaded, analyzed by the healthcare provider and discussed with the patient. However, it allowed treatment changes and has remained a useful educational tool.

CGM can also display glucose values continuously on a screen, and alarm limits can be set to allow immediate therapeutic

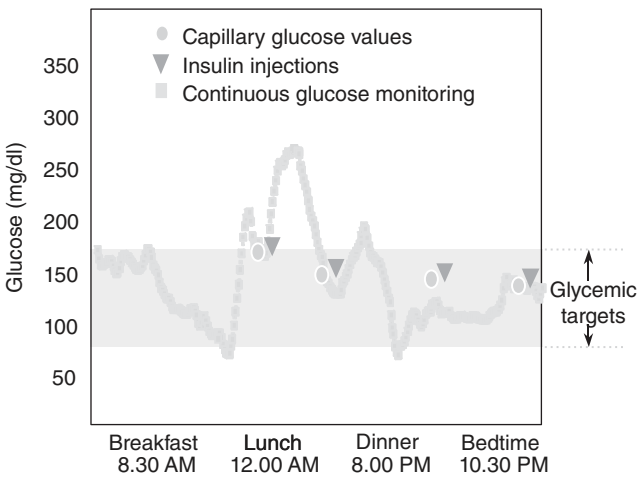

Fig. 2. Benefits of continuous glucose monitoring compared with self-monitoring of blood glucose: identification of undetected glycaemic fluctuations.

adjustments on the basis of real-time glucose results, thus avoiding glycaemic variability ("open loop"). Also, low-blood-glucose alarms can prevent hypoglycaemia, especially at night. Mandatory requirements include accuracy without too-frequent recalibration by the user [5,17]. However, interstitial glucose fluctuations and levels are not perfectly correlated with capillary glycaemia. Increased glycaemia may be observed with a delay at the interstitial glucose level. On the other hand, when sugar is decreasing, interstitial glucose decreases more rapidly, yet the technical delay can slow the results by up to around 10 min. For this reason, the ADA recommends verification of capillary glycaemia before each treatment modification (insulin correction, snacks) and in cases of "weird" results [18].

CGM technology provides a basis for insulin administration at more appropriate dosages and timing for patients using real-time monitoring. At present, a reduction of 0.3-0.6% in HbA_{1c} can be expected with CGM in the patients considered "responders" [17]. Benefits have been shown at 3 months [17,19] and confirmed at 6 months [20-22], and appear to be higher in compliant, previously well-controlled, pump patients [23]. In a study comparing CSII with and without CGM [20], the benefits were found to be significantly greater in patients wearing the sensor for > 70% of the time and modifying their diabetes management (real trend) accordingly. These observations may explain in part the greater benefits seen in adult patients aged > 25 years compared with adolescents [21,24]. Also, adherence to CGM over the first 3 or 4 weeks is predictive of compliance ultimately [24], so a 1-month CGM trial should perhaps be proposed for all patients who wish to try it.

One study showed a significant decrease in hypoglycaemia frequency coupled with HbA_{1c} improvement with CGM [23]. However, no difference in quality of life was noted, although some parameters, such as "fear of hypoglycaemia", were improved [25]. Patients' education and, thus, care-provider training is mandatory to teach the most appropriate reactions to "real-time data" to avoid overreactions that can lead to wide glycaemic fluctuations and increased anxiety [26].

5. Insulin administration: from injections to perfusion?

After the discovery of insulin and its synthesis, diabetes therapy began to use several insulin injections of regular non-modified insulin. The addition of zinc and protamine led to long-acting insulins that allowed a reduction in the number of insulin shots. Injections were given using needles and syringes that had to be boiled prior to use (Fig. 1B), but these materials have become more and more user-friendly over time such that, nowadays, most insulin pens are prefilled devices needing limited manipulation, and use very small needles (5-8 mm) that are almost painless. This comfort for the patient, coupled with the use of insulin analogues, has allowed the development of intensive treatments such as the "basal-bolus" regimen.

CSII begun in the 1970s [27, 28], and enables treatment to mimic physiological insulin basal secretion by adapting infusions to 24-h circadian needs, which are generally lower between midnight to 4AM, and the dawn phenomenon.

Insulin pumps are small devices programmed to infuse insulin through a catheter inserted under the skin. Insulin injections, even with rapid-acting analogues, often induce glycaemic fluctuations due to variations in injection sites and depths. CSII ameliorates these parameters. The constancy of basal delivery allows a near-flat blood insulin profile and is adjustable at preset times to suit the changing needs of the patient throughout the day [29]; it also allows good reproducibility in the same patient. With CSII and the other technologies, patients can adapt to near real-time modifications (so-called "open loop") [30]. Insulin infusions can be modified at any time – in case of, for example, unexpected exercise – with a secondary transient basal rate. Different studies have demonstrated the superiority of CSII coupled with analogues in terms of HbA_{1c} and hypoglycaemia compared with multiple injections. Insulin pump therapy is now the "gold standard" for T1D intensive insulin therapy [29].

The frequency of severe hypoglycaemia is reduced by about 75% with CSII [29]. Two meta-analyses [31,32], involving 600 and 1547 patients, respectively, confirmed a -0.5% improvement of HbA_{1c} with CSII in association with a decrease in insulin doses. Also, programmable pumps have led to improved preprandial glycaemic control and fewer episodes of overnight hypoglycaemia [33]. In addition, studies evaluating depression and quality of life have shown either benefits or neutral effects with CSII [31,32].

The main risk of CSII is ketoacidosis due to the lack of a subcutaneous insulin depot. Undetected insulin infusion interruption due to catheter obstruction, needle displacement or pump dysfunction is another cause for concern, especially at night or during pregnancy [5]. However, studies have shown a lower number of ketoacidosis episodes in CSII-treated patients [34,35].

Nevertheless, CSII remains a complex therapy: some patients are reluctant to wear a pump at all times as it reminds them of their disease; blood glucose measurements have to be performed at least four times a day to adapt basal rates and boluses; and ketonaemia has to be checked before going to bed to detect any pump malfunctions. Another limitation of CSII is the complexity of device usage, especially for older and blind patients. Nowadays, however, pumps are more user-friendly and more like cell-phone devices.

CSII has also been considered in recent years as a potential treatment for improving blood glucose control in uncontrolled T2D patients using basal-bolus regimens, as it can reduce HbA_{1c} levels and daily insulin requirements [36,37]. Quality-of-life scales are also improved, in particular, the anxiety and burden scales. However, it still remains more controversial.

In children and particularly in neonates, CSII compared with multiple daily insulin injections (MDI) results in better metabolic control [37]. CSII allows very low-dose insulin delivery and, in adolescents, quality of life is improved by permitting more flexibility in meals and physical activities. The dawn phenomenon, frequently seen in adolescents, is also easily compensated for. The insulin-delivery history function allows clinicians and parents to verify whether insulin delivery

has been properly done and no bolus omitted, and an alarm reminds users that it is "bolus time" [38, 39].

Others indications of CSII include pregnancy in T1D patients, insulin allergy and lipoatrophy. In addition, CSII has also proven its efficacy in transitory indications such as hyperalgesia in neuropathy, infections and wound-healing. It can also help to rapidly decrease glucotoxicity in uncontrolled diabetic patients.

In general, pumps are now safer, their alarms can alert users to electronic failure or increased catheter pressure, basal rates can be changed every few hours, and boluses can be normal or square wave, or a combination of the two, to adapt to different types of meals.

A new feature, a bolus calculator called "Bolus Wizard", determines bolus doses based on data input from the wearer, such as the patient's current blood glucose, target blood glucose, evaluated amount of carbohydrate consumed, insulin sensitivity and insulin-to-carbohydrate ratio, as well as insulin action duration ("insulin on board") [40]. In 2008, Shashaj et al. [41] showed that, in paediatric patients, the bolus insulin dose calculated by Bolus Wizard was effective for improving pre- and postprandial glycaemic control, with fewer correction boluses, no differences in prandial insulin requirements and no restriction in the carbohydrate content of meals. Also, patients reported that using Bolus Wizard was easy and associated with a high level of satisfaction.

CSII limitations are essentially its cost and the education necessary for its proper use. Patients' motivation and skills also need to be regularly evaluated, for example, by an annual therapeutic efficacy evaluation for every patient. Recent cost– benefit analyses have concluded that CSII is cost-effective when it induces improvements in both glycaemic control and chronic complications [42-44].

Contraindications to CSII are essentially severe psychiatric disorders, patients' inability to use the device, and activities involving extreme conditions such as cold, heat, scuba diving or exposure to magnetic fields such as magnetic resonance imaging.

Nevertheless, despite these technological improvements, the fear of hypoglycaemia is one of the main limitations for intensive insulin therapy to achieve HbA_{1c} goals in diabetic patients [45]. The Paradigm® Veo™ pump is linked to a glucose sensor that shuts down when glycaemia is under a certain limit, and restarts after 2h. This may be the beginning of a solution for patients with hypoglycaemia unawareness, especially at night. However, no randomized study has been carried out with this device. Its limitations could include the risk of very high glycaemia when insulin is stopped after a hypoglycaemic episode, and the risk of restarting the pump when no capillary blood glucose has been performed.

6. Continuous peritoneal insulin infusion

This route of insulin infusion allows insulin to be absorbed by the physiological portal route. This means that insulin absorption is rapid compared with subcutaneously administered insulin analogues, and more reproducible [5]. Insulin first absorbed in the liver normalizes a number of proteins synthesized by the liver through insulin regulation, such as lipoproteins, plasminogen activator inhibitor-1 (PAI-1) and insulin-like growth factor-1 (IGF-1). Thus, glycogen storage is increased in the liver, and peripheral insulin levels are lower, thereby reducing the frequency of glucose variations and, consequently, severe hypoglycaemia. Implantable devices are used to avoid peritoneal infections; these are composed of a casing containing the pump system, a negative-pressure insulin reservoir and a two-layer silicone catheter. An external communicator enables remote control of the device by telemetry [5]. The use of a specific insulin stabilizer is mandatory, however, to avoid insulin aggregation and pump blockages [46].

Indications for this insulin delivery system are limited to T1D patients who remain uncontrolled despite well-managed CSII and certain, rare, cases of subcutaneous insulin resistance.

Pumps are implanted during a surgical procedure and need to be replaced every 7 years (the average lifetime of the battery). The main complications are telemetry disconnection, catheter blockages, electronic pump dysfunction and pump blockages due to insulin aggregates; however, such accumulations are unusual and are usually solved by rinsing the pump *in vivo*, using a basic solution.

This mode of insulin administration may be one of the steps towards closing the loop.

7. Closing the loop: advances in pump therapy and continuous glucose monitoring

On the basis of insulin administration regulated by real-time glucose levels determined by a glucose sensor using mathematical algorithms, the first artificial endocrine pancreas [47] involved a double-lumen catheter that allowed continuous glucose measurement of venous blood, using a microcomputer and an intravenous insulin infusion. The Biostator GCIIS [48] became commercially available and was used for hospitalized fasting patients in numerous clinical studies to determine insulin sensitivity and circadian needs using a glucose clamp technique. The technology was highly effective but was, of course, never used for clinical diabetes management.

Many factors need to be taken into account when creating mathematical algorithms adapted to ambulatory, meal-taking patients, including insulin pharmacokinetics and pharmacodynamics, glucose metabolism, glucose concentrations in blood interstitial fluid and insulin resistance. Some studies have shown good responses in basal situations, but results have been less satisfactory at mealtimes [49]. Different sites have also been evaluated, such as intraperitoneal or subcutaneous insulin infusions combined with a subcutaneous or intravenous sensor [49, 50]. Indeed, the feasibility of a closed-loop system of insulin delivery using a subcutaneous glucose sensor and intraperitoneal insulin delivery, *vs* an open-loop system in T1D patients has been evaluated [49].

In hospitalized patients, significantly higher postprandial glycaemia, but lower average glycaemia, were observed; improvements in glucose control were also noted during extraprandial periods and in interindividual postprandial or nocturnal variations. Hypoglycaemia rates were low and comparable between the two groups. This study suggests that better glycaemic control with closed-loop insulin delivery is feasible. In addition, nocturnal closed-loop insulin delivery would clearly be clinically relevant for preventing nocturnal hypoglycaemia.

In most studies, glycaemic between-meal results are usually satisfactory, whereas postprandial periods have failed to fulfill requirements despite the use of various algorithms and insulin infusion routes [51, 52]. This might be explained by the cephalic phase of insulin secretion, the incretin effect, and the variability of intestinal absorption and the glycaemic index. Given the prandial-state limitations, a "partial open loop" was proposed by Weinzimer et al. [51] to control postprandial hyperglycaemia, and demonstrated significantly lower postprandial glucose levels with the hybridized system (manual bolus plus automatic bolus) compared with the fully automated system.

8. Can the development of telemedicine replace the human healthcare provider?

Health authorities have high expectations for telemedicine (TM), as it addresses several major challenges, such as improving access to healthcare, especially in underserved or remote areas; overcoming the lack of specialists facing the diabetes epidemic; and reducing the costs of healthcare while improving its quality. The aims of TM in diabetes, however, differ according to the type of diabetes [53].

In T1D, despite optimalized insulin treatment, proper follow-up, education and compliance, many patients' HbA_{1c} values remain persistently > 8% [54]. Leaving aside the relatively rare cases of authentic instability, these poor results may be explained, at least in part, by the difficulties faced by patients in coping with the burden and complexity of the disease, such as properly applying the complex rules of calculation of their prandial and basal insulin doses, keeping a logbook and having regular consultations with their physician [53]. Physicians themselves often face a lack of information during the consultation, with no data on which to base their advice regarding the patient's insulin dose adjustments.

In T1D, the goal of TM is to help patients to achieve better control of their blood glucose levels through accurate adjustments of their insulin doses. Teletransmission of glycaemic data to a care provider, who sends feedback to the patient, is one of the main tools of TM. Several studies [55-57] have shown conflicting outcomes, with improvements in diabetes control not always being significant. One limitation of the method is the possible lack of the different parameters needed to adjust insulin doses (meals, previous insulin doses, activities). Thus, an active electronic diary kept on a smartphone that allows automatic teletransmission of data such as blood glucose, insulin doses, dietary data and details of physical activity may be more attractive than a traditional diary [53]. Data stored on a mobile phone can be periodically sent as short messages and reviewed by physicians on their computers, and new prescriptions may then be sent back. Alarms set up by physicians can be incorporated such that, when high or low blood glucose is detected, the data and alarm will be automatically sent to the physician [53]. The Diabeo system [58, 59] produced good results in terms of blood glucose improvement and patients' satisfaction. At the end of the study, a large majority of patients wished to continue using the system, even at their own expense, rather than returning to a traditional passive diary.

The same tools may be used in T2D, although the impact of SMBG on glucose control is more controversial in this considerably larger diabetic population. T2D requires not only treatment adjustments, but also behavioural changes (control of calorie intakes and regular physical activity) that appear to be best established through regular coaching from caregivers. One study [60] has shown that educational messages were as efficient for individual consultations as video-conferencing, with an HbA_{1c} of 7.8 ± 1.5% in both groups immediately after the educational programme that remained comparable 3 months later.

Many TM studies focusing on the management of blood glucose levels have been published, but the majority have failed to demonstrate any superiority of TM *vs* traditional care. Three prerequisites are needed for success [53]. First, systems need to be easy to use on readily available, pocket-sized, electronic devices. Also, patients' questions have to be answered quickly, as feedback delay has accounted for the poor performance of many systems. In addition, easy interactivity with a known caregiver is important, as it explains both the good results achieved with TM systems using teleconsultations, and the poorer results when human contact consists of only texting or e-mails and when the patient is unknown to the care provider.

Active electronic diaries could replace traditional logbooks, and could allow insulin doses to be proposed based on the automatic application of algorithms coupled with automatic alarms sent to physicians in case of major glucose variations. Glucose readings could then be automatically transferred to a smartphone, pending a direct connection with the glucose sensor and a return of control of the insulin pump, thus forming a closed loop [53].

However, effective TM programmes are expensive and time-consuming, and require reorganization of the healthcare system. It would also be useful to involve nurses and other caregivers specialized in diabetes to ensure adequate education and TM system management under the control of the referring physician. Also, because of the growing number of T2D patients, it will be necessary to identify the most distressed patients likely to benefit the most from targeted interventions.

Thus, TM is a valuable tool, but it cannot completely replace human care providers and physicians. Moreover, the technology is not accessible to all patients, as elderly people are often incapable of coping with such systems.

9. Conclusion

The treatment and follow-up of diabetes have dramatically improved over the past century. Changes have tended to improve glucose management towards achieving near-normal glycaemia while avoiding chronic complications, and have also tended to improve patients'quality of life. All devices comprise one of the steps towards the concept of "closed-loop insulin delivery", which will free patients of glucose control and parenteral self-monitored insulin administration. However, at present, around 30% of T1D and T2D patients are far from achieving their defined glycaemic goals. Diabetes still remains a complex chronic disease that makes it a true burden for patients in their day-to-day lives. Attention, empathy and personal involvement are still the main tools for motivating and supporting the patients who suffer from this chronic disease. Nevertheless, these innovative technologies are to be considered only tools, and not replacements for human skills.

Conflicts of interest statement

N. Jeandidier: investigator (Abbott, Lilly,Medtronic, Novo) ; investigator and expert (Sanofi Aventis) ; board (Novo Nordisk).

M. Pinget: advisory services (Medtronic, Roche Diagnostic et Ypsomed) ; participation, for the past twelve months, to national and international boards (MSD, Medtronic, NovoNordisk, Sanofi-Aventis) ; Conferences: attendance as contributor for the past twelve months to national and international symposiums (Astra-Zeneca, BMS, Medtronic, MSD, Novartis, NovoNordisk, Pfizer).

F. Moreau: investigator (Medtronic, Abbott) ; expert (Lilly, Lifescan) ; consultant (BMS) ; attendance (congress) (Lilly)

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Emergent technologies applied to diabetes: What do we need to integrate continuous glucose monitoring into daily practice?

Where the long-term use of continuous glucose monitoring stands in 2011

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Abstract

The earliest continuous glucose monitoring (CGM) devices did not permit real-time readouts of glucose measurements. Instead, they were used to determine the glucose profile of patients in "real life" and as educational tools. In contrast, the latest real-time devices, whether linked or not to an insulin pump, give the patient access to glucose measurements and incorporate alarms that can be set. Thus, they are the newest self-management tools for patients with type 1 diabetes requiring an intensive insulin regimen. Some long-term studies in a selected population of patients with type 1 diabetes have shown improvement of glycaemic control as measured by HbA_{1c}. Although the characteristics of "responsive" patients have yet to be identified, the ability of the patient to use the system on a near-daily basis (about 80% of the time) is a key point. Initial training of the patient by a professional team with expertise in CGM is also of the utmost importance. To date, CGM is not reimbursed by Social Security in France.

Keywords: *Type 1 diabetes; Continuous glucose monitoring; Intensive insulin regimen; CSII; Insulin pump; Therapeutic education; Interstitial glucose; Review*

Résumé

Mesure continue du glucose: où en sommes-nous en 2011 ?

Les premiers systèmes de mesure continue du glucose (CGM) ne permettaient pas l'accès en temps réel aux données glycémiques. Il s'agissait d'outils d'exploration du profil glycémique dans le milieu de vie habituel du patient et d'outils d'éducation. Les derniers systèmes, couplés ou non à une pompe à insuline, affichent les données glycémiques en temps réel et permettent de régler différentes alertes. Ils deviennent donc un outil à la disposition du « patient » diabétique de type 1 sous traitement intensifié. Les études au long cours montrent une réduction de l'HbA_{1c} lors de l'utilisation de la CGM dans une population sélectionnée de patients diabétiques de type 1. Les caractéristiques des patients « répondeurs » ne sont pas bien identifiées mais l'aptitude du patient à utiliser le système de CGM de manière assidue (près de 80% du temps) est un élément clé du succès. La formation initiale spécifique du patient par une équipe experte dans le domaine est également capitale. La CGM n'est pas encore prise en charge par l'assurance maladie en France.

Mots clés : Diabète de type 1 ; Mesure continue du glucose ; Schéma basal bolus ; Pompe à insuline ; Éducation thérapeutique ; Glucose interstitial ; Revue générale

1. Introduction

Continuous glucose monitoring (CGM) devices provide an estimated value of blood glucose by measuring interstitial glucose and using mathematical algorithms. Every 5 min, a new measurement is available, resulting in 288 measurements a day. However, CGM does not obviate self-monitoring of blood glucose (SMBG), for which the device has to be calibrated one to three times a day. The first CGM devices were approved by the US Food and Drug Administration (FDA) in 1999. With those delayed-readout devices, the patient remains unaware of the glucose measurements until they are downloaded. In contrast, with the latest real-time devices, glucose values are continuously available to the wearer. Each device comprises a

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sensor, transmitter and receiver (Fig. 1). In certain cases, the receiver can be an insulin pump (Paradigm Veo®, Medtronic; Animas Vibe®, Dexcom); in other cases, it can serve as a regular glucose meter (Navigator®, Abbott) (Fig. 2). If the receiver is a pump, there are as yet no automated adjustments made to the insulin infusion based on the glucose values obtained by CGM (closed-loop system).

2. Short-term glucose monitoring on demand

The short-term use of a CGM device or "glycaemic Holter" makes it possible to collect the glucose profile of a patient in real life over 3 to 5 days. The data are then downloaded and analyzed. The choice of a real-time or delayed-readout device is determined by the indication being monitored. Review of the CGM results is a helpful teaching tool that enables the patient, with the help of the health-care professional, to appreciate the effects of food, insulin timing and exercise on glucose levels. It can also provide diagnostic and management advice. However, the contribution of short-term CGM to better metabolic control remains unreliable and often disappointing [1].

Fig. 1. Continuous glucose monitoring devices consist of three parts: a sensor, a transmitter and a receiver which can be linked to an insulin pump or not. (1) the sensor (electrode); (2) the transmitter (radio frequency); (3) the receiver.

3. Long-term CGM

Real-time readout devices are used for the long term (Fig. 2). The glucose results are continuously available to the wearer, as is the rate of change in estimated glucose levels (trend arrows). Also, the devices can be set so that an alarm alerts the wearer to a glucose value that is projected to fall below or above the target within 10-30 min, based on the rate of change of interstitial glucose (Fig. 3). CGM provides information on glucose variability over periods of time that are seldom or never explored by SMBG (such as at night and post-meals). As hyperglycaemia and asymptomatic hypoglycaemia are detected by the device, the patient is alerted, thereby preventing their occurrence.

The reliability of the measurements makes it possible to use CGM in current practice; according to the manufacturer, the Medtronic Enlite® sensor has a mean absolute percent difference of 14.1% between the estimated glucose value and venous plasma glycaemia. However, during periods of rapid changes in blood glucose, there are time-lag errors between the interstitial-space glucose measure and SMBG. This is the case after meals, after supplementary insulin injection or after sugar intakes to correct low blood glucose, and it needs to be considered when reviewing the data [2]. The American Diabetes Association (ADA) [3] recommends SMBG before making any immediate management decisions (supplementary insulin, sugar intake).

4. Selecting patients for the best outcomes

Any patients with diabetes requiring an intensive insulin regimen are potentially good candidates for this technology. A number of randomized controlled clinical trials have been

Fig. 2. Real-time CGM devices available in France in 2011.

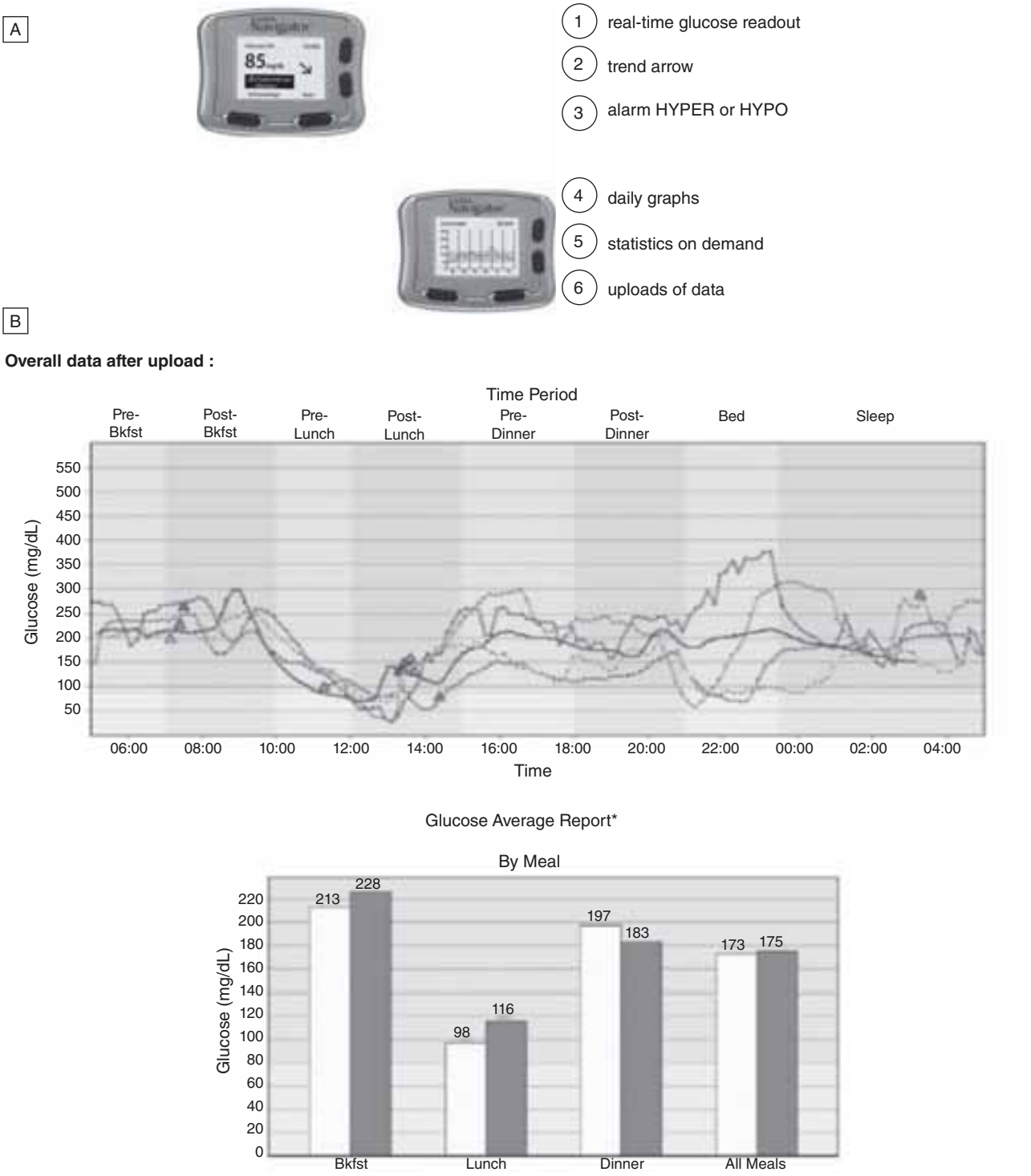


Fig. 3. Information available on a real-time device. Navigator®, Abbott. Data before (A) and after (B) upload.

undertaken to evaluate the impact of CGM in patients with type 1 diabetes, mostly using an insulin pump or multiple daily injections (MDI). Depending on the trial, HBA_{1c} was reduced by 0.30–0.60% in "good candidates" [4]; this benefit was present at 3 months [5,6], and was also confirmed at the 6-month [7-9] and 1-year follow-ups (the *Capteur-Evadiac* study, publication in progress).

Frequent personal use of the system is a key determinant of success [7,8]. The best outcomes are observed when the CGM device is used > 70% [7,10] or 80% [5,7,8] of the time. The more consistently CGM is used, the greater the metabolic benefits [11]. The near-daily use of CGM yields more information that patients can incorporate into their diabetes management, but it can also serve as a marker for patients who are more engaged in their

diabetes self-management. In the Juvenile Diabetes Research Foundation (JDRF) trial [8], the benefit to glucose control could be observed only in adults aged over 25 who made more sustained use of the device than did younger patients: 83% of the subjects over 25 used it on 6 or more days a week *vs* 30% of those aged 15-24 years [11]. However, in patients < 25 years of age, greater CGM use was associated with a similar reduction of HbA_{1c}. In the same trial, none of the psychosocial variables studied were predictive of the frequency of CGM use [11].

Before randomization, patients were performing an average of more than four blood glucose measurements per day, and their mean HbA_{1c} ranged from 6.9% to 9.6% [5,8,9,12]. Also, CGM is not confined to patients with insulin pumps, although, in one trial, an additional benefit was found in patients using a pump *vs* MDI (*Capteur-Evadiac*, publication in progress). On comparing patients using a sensor-augmented insulin pump with those using MDI and SMBG, decreases of 0.6% ($P < 0.01$) [10] and 1.1% ($P < 0.001$) [13] in HbA_{1c} were found. Supplementary benefit was observed after CGM use in patients with type 1 diabetes who had already achieved excellent control of their HbA_{1c}, with levels at 6.5% [14] and 6.9% [9]; HbA_{1c} was reduced by 0.27% with no increase in severe hypoglycaemic events, and less time was spent below 60 mg/dL [13] or 70 mg/dL [9].

Nevertheless, evidence of the benefits of CGM in certain populations is lacking. There has been no randomized study of patients with poorly controlled diabetes or of those who perform little or no SMBG. There are also scarcely any studies [15] supporting the benefit of CGM during pregnancy, or in patients with hypoglycaemia unawareness and/or frequent severe hypoglycaemic events. The bulkiness of the CGM devices (even when miniaturized) and the alarms can impair patients' quality of life. However, in the JDRF study, no evidence was found of any changes in quality of life [16], although certain indicators of well-being were improved (*Capteur-Evadiac*, publication in progress). In addition, there was a reduced fear of hypoglycaemia in adult patients [16,17].

Furthermore, the impact of CGM on patients with diabetes is yet to be explored. The characteristics of responsive patients – those most likely to benefit from CGM use – are not yet known. As a high degree of early use (during the first 4 weeks) may be a predictor of sustained long-term use [11], a 4-week trial of CGM should be made available for patients who request it.

5. Patients' training with CGM: What is the key to success?

Together with the selection of appropriate patients, the training of health-care professionals is an important precondition of success. This was emphasized by the authors of the Small Troubles, Adaptive Responses (STAR-1) study [18], who partly attributed the failure of CGM in their study to the novelty of the tool and the insufficiently trained health-care team.

In addition, the training of patients should be both technical – to provide the required knowledge of the device – and educational – for better diabetes self-management. The basic knowledge of diabetes self-management should also be supplemented by training in functional insulin treatment (different types of insulin, delay in action of insulin, algorithms for the correction of high blood glucose, prevention and treatment of low blood glucose) [19,20].

As a glucose value is available every 5 min, it is clear that special training is required to properly analyze and apply the information. At the start of CGM, patients should undergo a specific educational programme delivered by a well-trained professional. This takes time and should be considered in the organization of the health-care team's schedule. Training should provide information about the device, such as the requirements for calibration, and details of the time delay between SMBG and CGM values during periods of glucose variation [21]. Information on the glucose trend arrow should also be explained and emphasized. Also, algorithms for making diabetes management decisions using glucose values have been proposed but, so far, there has been no consensus on their use [21-24]. If an aberrant or unexplained result shows up on the device, the accuracy of the device needs to be questioned and SMBG performed.

There are different ways to use CGM, ranging from the simple use of alarms to prevent severe hypoglycaemic events in patients with hypoglycaemia unawareness [25] to the intensive use of the data for real-time adjustments to insulin doses and retrospective (after uploading the data) decisions for diabetes self-management. However, the unnecessary prescription of CGM or insufficient training of the patient can lead, at best, to unjustified extra costs and, at worst, to risks to the patient due to misuse of the data (such as iterative supplementary insulin injections or inappropriate sugar intakes) and inappropriate therapeutic decisions (Fig. 4) [26]. For these reasons, an educational diagnosis prior to the prescription is mandatory.

Follow-ups with a health-care professional, such as a face-to-face meeting, require the allocation of extra time. The use of telemedicine [27], at least at the start of CGM, could be a time-saver. Review of the downloaded data makes retrospective adjustment of insulin doses possible, and also determines the accuracy of decisions made by the patient in terms of supplementary insulin, sugar intake and management of physical activities. If the patient is using a sensor-augmented insulin pump, the insulin profile is superimposed on the glucose profile. In a motivated patient, this can lead to improvement in the glucose profile after 6 days of CGM (Fig. 5).

To date, there are hardly any automated interactions between the results of CGM and the rate of insulin infusion by the pump. However, one function in the Paradigm Veo pump enables a 2 h suspension of insulin infusion if the CGM value falls below a programmed glucose level. Some studies [28] have favoured the efficacy and safety of such a function, but further studies are needed on the subject. The ADA [3] and the American Association of Clinical Endocrinologists [29] have published some guidelines, while French guidelines [by the French Society of Diabetes (*Société Francophone du Diabète*)] are still in the process of being written.

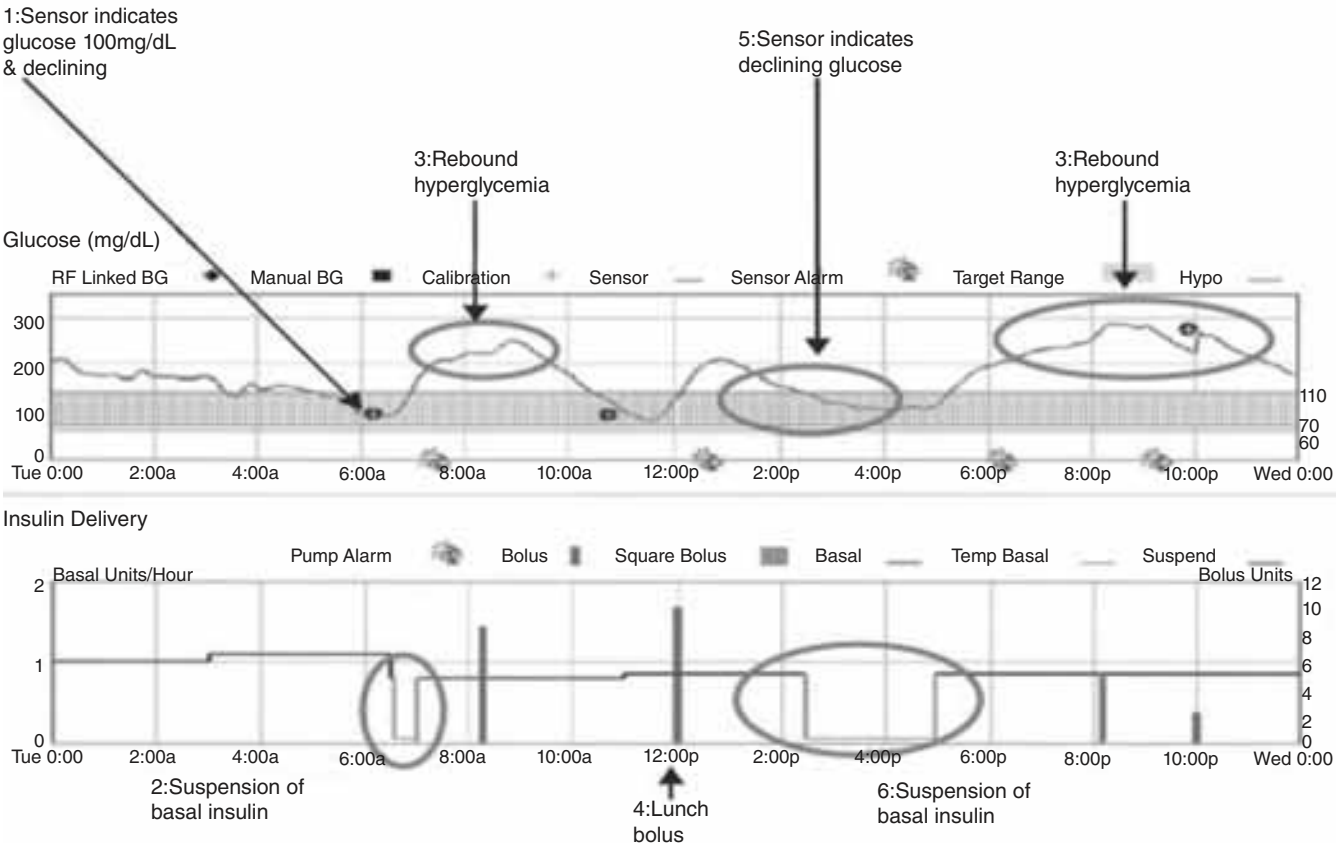
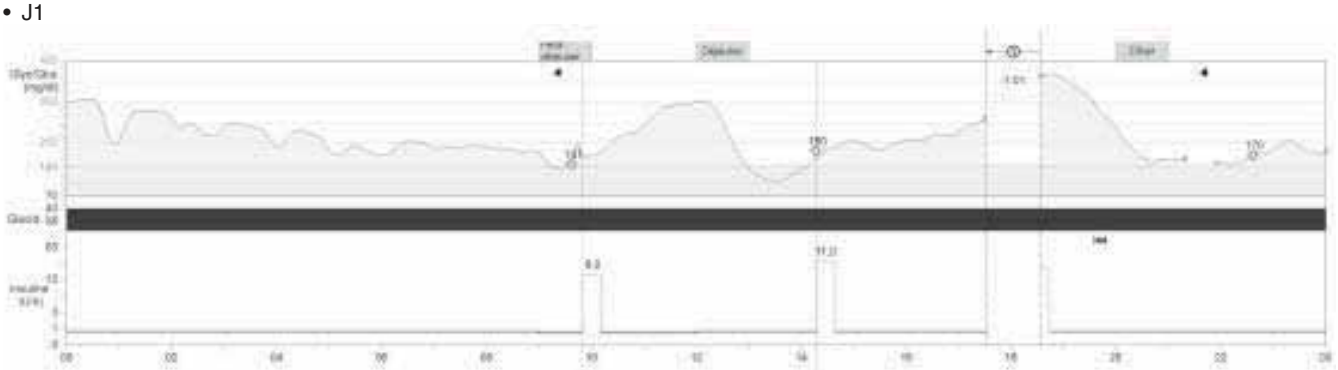


Fig. 4. A patient misuses CGM: inappropriate interruption of the basal infusion of insulin in a patient with a pump (from [26]).

• J1



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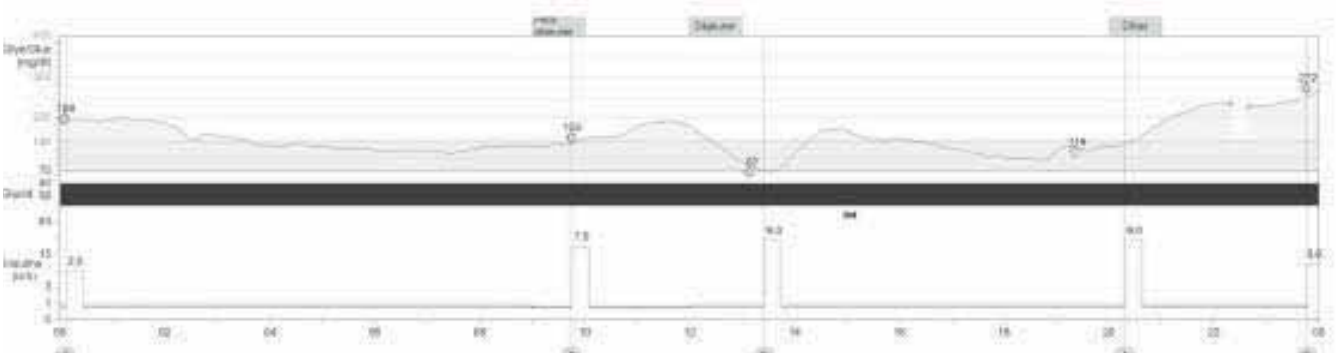

Fig. 5. A patient masters the use of CGM: example of an improvement of the glucose profile after 6 days of use.

6. Conclusion

The use of CGM devices can bring about metabolic improvements in some patients with type 1 diabetes requiring an intensive insulin regimen. Therefore, to implement the daily use of CGM in outpatients with the best cost/benefit balance, it is necessary to target those patients who are most likely to benefit from the technology. The metabolic benefits are correlated with sustained use of the device for more than 80% of the time. A trial of CGM should be made available to patients with type 1 diabetes to identify responsive subjects. It is absolutely necessary that the training and initial steps in the use of CGM be guided by a health-care team that is experienced in the education of diabetic patients and well schooled in CGM. Also, during the first trimester, the benefit to the patient of keeping the device should be evaluated. Last but not least, access to the device by all concerned patients will depend on its being reimbursed by Social Security. A recent study suggests that, among the appropriate targeted patients, CGM has a favourable cost/benefit rate [30].

Conflicts of interest statement

No conflict of interest to declare in relation with this article.

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Diabetes & Metabolism 37 (2011) S71-S77

Telemedicine: What more is needed for its integration in everyday life?

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Abstract

The Health Authorities have huge expectations of telemedicine (TM): improved patient access to healthcare, a solution to the shortage of doctors in the face of an exponentially expanding disease, and reduced healthcare costs with improved quality.

There are a host of applications for TM in the area of diabetes. TM has been validated and has been widely used to screen for diabetic retinopathy, and a number of studies are currently underway for the follow-up of diabetic foot ulcers. However, the main indication of TM remains the follow-up and control of blood glucose. In this area, many studies have been conducted to improve glycaemic control. While most of these studies have failed to show any benefits vs. conventional care, a small number have demonstrated great efficacy of this approach with regard to glycaemia. Using these studies, we attempt to define the key qualities of a successful TM system.

How can we extend the results of these experiments beyond the framework of clinical studies and integrate them in daily practice so as to improve diabetes management?

This is the key challenge for TM, implementation of which will require reorganization of healthcare, given the evolution of medical demographics. This reorganization will involve healthcare providers specialized in diabetes that may intervene in assigning physicians for especially distressed patients. However, such reorganization will require medico-economic evaluation before it can be implemented on a larger scale.

Keywords: *Telemedicine; Type 1 and type 2 diabetes; Medical device; Smart-phone; Education; Organization of healthcare; Review*

Résumé

Télémédecine: que manque t-il pour l'intégrer au quotidien?

Les attentes des Autorités de Santé vis-à-vis de la télémédecine (TM) sont considérables : améliorer l'accès aux soins des patients, pallier à la pénurie de médecins face à une maladie dont la prévalence explose et réduire les coûts de santé tout en en améliorant la qualité.

Les champs d'application de la TM dans le domaine de la diabétologie sont nombreux. La TM est déjà largement utilisée pour le dépistage de la rétinopathie diabétique et des expériences sont en cours pour le suivi des lésions de pied. Sa principale indication reste toutefois le contrôle de la glycémie. Dans ce domaine, de nombreuses expériences ont été conduites visant l'amélioration du contrôle glycémique. Si la plupart d'entre elles ne sont pas parvenues à montrer de bénéfice vs une prise en charge conventionnelle, quelques-unes, peu nombreuses, ont toutefois fait la preuve de leur efficacité. A travers elles, nous définirons les qualités indispensables d'un système de TM performant.

Comment ensuite sortir ces expériences du cadre des études cliniques et les intégrer au quotidien pour renforcer la prise en charge des patients diabétiques ? C'est là le véritable enjeu de la TM dont le déploiement devra passer, compte tenu de l'évolution de la démographie médicale, par une réorganisation de l'offre de soins avec l'implication de paramédicaux formés à la diabétologie qui pourront intervenir par délégation médicale auprès des patients identifiés comme en difficultés. Une telle organisation devra toutefois être évaluée sur le plan médico-économique avant d'envisager sa transposition à large échelle sur le territoire national.

Mots clés : Télémédecine ; Diabète ; Dispositif medical ; Smart-phone ; Education ; Organisation de l'offre de soins ; Revue générale

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1. Introduction

Health authorities currently have high expectations of telemedicine (TM). Telemedicine "can be a powerful lever for driving the restructuring of healthcare organization" as stipulated in the French HPST law (Hospital, Patients, Health, Territories). This is how the role of TM is presented within the "organization of healthcare" in the recent report of the DHOS [1] (Department of Hospitalization and of Healthcare Organization). The authors, P. Simon and D. Acker, define the four fields covered by telemedicine: tele-consultation, tele-expertise, tele-monitoring and tele-care. In the report, a major place has been accorded to diabetes. Generalists working in local institutions will be linked by telemedicine to specialists in reference institutions. The benefits of this type of approach with regard to certain cardiovascular (stroke, myocardial infarction) or metabolic (chronic renal failure, diabetes) emergencies are clear […]. The most costly diseases in terms of current management likely to derive benefit in terms of both quality and safety of care while reducing health costs through remote monitoring at the patient's home are: heart failure, kidney failure, diabetes and hypertension. Finally The French National Order of Physicians (CNOM: *Conseil de l'Ordre des Médecins*) has stated that "The act of telemedicine [is] an authentic medical procedure in itself" [2]. TM may serve a dual purpose: first, it may partly solve the problem of shortages of doctors, both specialists and generalists, as well as the problem of remoteness of many patients from healthcare centers in a context of limited budgetary resources. Second, it should also improve the quality of care thanks to the sophisticated electronic tools, now available. There are currently several possible applications for TM in diabetes :

- Transmission of information from a non-expert to an expert healthcare provider (HCP) with subsequent feedback in the opposite direction. A perfect application for such organization is screening for diabetic retinopathy, and possibly the follow-up and treatment of diabetic foot disease.
- The major application, however, is the provision of direct help to the patient, and in this case a different circuit is needed. Transmission of information from the patient to the caregiver and, after analysis of the data, feedback in the opposite direction with sending of instructions is far too time-consuming and cannot satisfy the immediate requirement. A two-level system is needed: 1) A "pocket" system for the patient that performs automatic analysis of the problem and provides an immediate automatic response based on preset algorithms determined by the caregiver, 2) Remote support by caregivers in predefined situations identified by automatic analysis of the data. For this TM application, a distinction must be made between type 1 [or type 2 diabetes treated with multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII)] and T2DM treated with dietary measures or oral antidiabetic agents (OADs), possibly along with a single injection of basal insulin.

2. TM and management of diabetes complications

Telemedicine has already been widely used in screening for diabetic retinopathy. Although the international guidelines recommend regular fundoscopy for all diabetic patients, access to an ophthalmologist may be difficult. Non-mydriatic fundus photography is now considered a valid method for assessing diabetic retinopathy (DR) and tele-medical networks using digital non-mydriatic fundus cameras have been developed. In France, OPHDIAT comprises peripheral screening centers equipped with non-mydriatic cameras, where fundus photographs are taken by technicians and linked by telemedicine to a reference centre in which the images are graded by ophthalmologists. Such networks have proved very effective for retinopathy screening, increasing the number of patients undergoing fundus examination and reducing the mean time required by an ophthalmologist for each diagnosis of diabetic retinopathy [3]. This type of organization enables optimization of care since ophthalmologists can focus on patients with retinopathy, cataract and/or non-gradable photographs (about a quarter of patients) [4]. TM should also be of particular interest in the monitoring of chronic foot disease, through photographs transmitted to a physician at a referral center who can in turn make recommendations to nurses providing daily care. A number of pilot studies are currently underway. Provided they can demonstrate medico-economic benefits, these experiments will be extended to larger populations of patients with diabetic foot disease.

Beyond screening and management of diabetes complications, TM has been used mainly in the control of blood glucose (BG).

3. TM and blood glucose control

Experiments focusing on BG control have been extensively detailed in a recent review [5]. We will focus on experiments that have either shown real benefits in terms of glycaemic control or that appear promising, in both type 1 and type 2 diabetes.

3.1. TM in type 1 diabetes

DCCT has already shown that close management of T1 diabetic patients partly based on monthly visits but also on regular phone contacts led to significant improvement in HbA_{1c} levels [6]. The same conclusion can be drawn from the study conducted by Thompson [7] in 46 insulin-treated diabetic patients with poor glycaemic control (HbA_{1c}>8.5%). A 15-minute phone call three times a week by a specialized nurse focusing on adjustment of insulin doses resulted in significant improvement in glycaemic control compared to standard care (from 9.6 to 7.8% vs. 9.4 to 8.9%, P<0.01). Although effective, this approach is time-consuming (17.25 h/w for 23 patients, for 6 months) and is thus unfeasible in large patient populations.

Systems involving uploading of BG values from a glucose meter with a memory function *via* the patient's cellular phone to the physician's computer with delayed feedback have

yielded rather disappointing results. While these tools, usually developed by firms that market BG meters, undoubtedly facilitate the caregiver's work by transmitting data in an easily accessible format, they rarely improve metabolic control. The weakness of the feedback chain to the patient (often *via* SMS) and the attendant time lapse may account for the negative, or at best, weakly positive, results. More complex systems involving a PDA instead of a phone have also proved disappointing in terms of metabolic control [8-10].

In type 1 diabetes, the way forward clearly involves active electronic diaries in smartphones that will effectively replace the traditional paper diaries. All of these embedded systems for patients on a basal-bolus insulin regimen incorporate a "bolus calculator" comparable to those used in insulin pumps. The latter provides the patient with immediate assistance in calculating prandial insulin doses at mealtimes, taking into account pre-prandial blood glucose value, carbohydrate load and level of physical activity, if any. The calculation is made on the basis of adjustment rules set by the physician. All data collected by the PDA are automatically transmitted to the caregiver and can be read on a computer screen, thereby allowing remote monitoring, and where necessary, provision of feedback to the patient, in accordance with the type of system used (*e.g.* SMS, phone consultations, e-mail). This dual feedback system allows day-to-day management of diabetes by the patient to be kept separate from longer-term supportive interventions by the HCP (motivational support). Two main systems have currently reached the stage of large-scale validation in populations of 130-180 patients.

The "Diabetes Interactive Diary" (DID) is a software package loaded onto a mobile phone that can help patients quantify their carbohydrate intake during meals by selecting the specific food and the amount consumed from a set of pictures. Like any bolus calculator, it can help patients determine the appropriate bolus of insulin needed based on the carbohydrate-to-insulin ratio and the insulin-sensitivity factor previously determined by the HCP. The system can also integrate additional data such as physical activity levels that require adjustment of either insulin dose or diet, and an algorithm has also been added for adjustment of the basal insulin dose. Data stored in the mobile device can be sent at regular intervals in the form of short messages and reviewed by the physician on his personal computer, and any new therapeutic and behavioral prescriptions can be sent from the physician's computer to the patient's mobile phone.

Despite these functions, studies to evaluate the DID have not yet shown any real benefit in terms of metabolic control. In the 3-month pilot study conducted in 50 fairly well-controlled T1DM patients (mean HbA_{1c}>7.2%) following a basal– bolus regimen, diabetes remained well controlled at the end of the study and the DID system was considered "excellent" or "good" by 96% of patients, and "extremely useful" or "very useful" by 72% [11]. The function considered most useful was carbohydrate counting using the electronic illustrated food list, followed by insulin-bolus calculation. However, the results of the validation study were rather disappointing [12]. This 6-month international, open-label, multicentre, parallel-group study was conducted in 130 T1DM patients not used to carbohydrate counting, with HbA_{1c} of between 7.5% and 10%, and randomized to either an intervention group (IG) or a control group (CG). Both groups showed a 0.5% reduction in HbA_{1c} (from 8.2% to 7.8% in the IG and from 8.4% to 7.9% in the CG), with no significant differences in terms of between-group analyses. Also, at the very most, the time devoted to carbohydrate-counting education in the IG was halved compared to the CG (6 h vs. 12 h, respectively; P=0.07) [13]. Although the provision of dual feedback to patients (consisting of: 1) automatic and immediate determination of carbohydrate intake and appropriate insulin dose; and 2) feedback from the HCP) initially appeared extremely valuable, the limited possibilities of expression *via* SMS may partly explain these first results. A multicentre, national, randomized parallel-group study involving 130 patients is underway to compare the impact of standardized DID education vs. usual practice on HbA_{1c} levels, incidence of hypoglycaemic events and glycaemic variability [14] (NCT01192711).

The second electronic diary on a smartphone is *the Diabeo system* developed through a partnership between the French Study and Research Centre for Improvement of Diabetes Therapy (CERITD) and Voluntis, an information technology and services company. In addition to the bolus calculator, based on the algorithms and glycaemic targets initially set by the physician, Diabeo also includes a basal insulin adjustment function that may be used even by patients on pump therapy with several different basal rates. One of its main novel features is an algorithm for self-improvement of functional insulin therapy (FIT) parameters based on blood glucose values. Again, this algorithm is preset by the physician. Finally, all data collected in the PDA can be transmitted to a secure website *via* GPRS, and authorized caregivers can consult the data directly in a readily interpretable format. This allows short but regular tele-consultations aimed at the reinforcement of therapeutic follow-up. Such consultations allow physicians to remain within the mean allocated time for each patient (approximately 30 min/patient/semester).

The first two evaluations of the Diabeo system conducted respectively in 10 and 35 DT1 patients showed good results for blood glucose profiles [15-16], with the same mean blood glucose values before and after each meal, reflecting the efficacy of both the bolus calculator and the algorithm for self-improvement of functional insulin therapy (FIT) parameters. Patient satisfaction was very good, with a large majority wishing to continue using the system even at their own expense, rather than returning to a traditional passive glycaemic diary. The 6-month multicentre randomized Telediab-1 study clearly showed marked metabolic improvement with the Diabeo system [17]. The study included 180 adults with T1DM on a basal-bolus insulin regimen (for >6 months and with CSII or MDI) with chronic poor blood glucose control (HbA_{1c}>8% twice consecutively, initial HbA_{1c} 9.1±1.1%).

These patients were randomized to three groups that were regularly monitored respectively by: 1) quarterly face-to-face consultations (G1 = control group); 2) the Diabeo system with quarterly face-to-face consultations (G2); and 3) the Diabeo system coupled with brief fortnightly telephone consultations (G3). Patients in G2 showed a 0.7% improvement in HbA_{1c} ($P<0.01$) at 6 months compared with the G1 controls, whereas in G3 (Diabeo system plus tele-consultations), HbA_{1c} was reduced by 0.9% ($P<0.001$) vs. G1, with no increase in the incidence of hypoglycaemia. In the latter group, the total time spent by the physician on telephone consultations was similar to the time spent on face-to-face consultations in the first two groups (1.2 h), but far less time was "lost" by patients on their consultations in G3, in addition to which there were no transport costs and no lost work time. This system is now routinely available and accessible to all patients equipped with a smartphone who wish to have it. There have been some developments concerning both the embedded system (smartphone) and the website. A major change involves the introduction of automatic analysis of patient data with identification of potential difficulties for the patient (failure to comply with the proposed insulin dose adjustment, no transmission of data within a given period, etc). This generates a warning to the HCP, who can then call the patient and mainly encourage them to start using the system again (if they so wish, of course) so as to benefit both from the insulin doses automatically proposed according to preset parameters and from the self-adjustment of these parameters in the event of BG values outside the target range. The automatic warning system prevents the HCP from being overwhelmed with too much data, which is unmanageable in practice, and allows him to target his actions on those patients having the greatest difficulty in coping with their diabetes treatment, while streamlining his available time. Compatibility of the Diabeo system with the main industrial standards is currently being implemented, and discussions are ongoing with the French national health insurance agency regarding reimbursement levels for the system.

3.2. What about TM for T2D diabetes?

Given the large number of patients with T2DM, efficient management of T2 diabetes using an adapted TM device should be of particular interest to optimize care in a context of limited budgetary resources.

Experiments with telephone consultations have been conducted in large populations of T2DM patients. They have necessarily led to attempts to focus the activity of nurses on those patients identified as the most distressed. In a randomized study by Piette et al. [18] involving veterans with diabetes, the IG (n = 124) received a series of automated telephone assessments to identify the most distressed patients likely to derive the greatest benefit from targeted intervention by a nurse (telephone monitoring). The nurse was not present at the clinic and had no direct physical contact with patients or indeed access to their medical records. The intervention was centered on blood glucose results and provided general educational information. The CG group (n = 124) was followed up as usual (traditional care). HbA_{1c} values at baseline were similar between the two groups (IG vs. CG: 8.8±1.8% vs. 8.6±1.8%) and the 12-month assessment showed no differences (ΔHbA_{1c} [IG vs. CG] = -0.3%; P = 0.1). The number of IG patients achieving an HbA_{1c} level <7% was twice that in the CG (17% vs. 8%, respectively; P = 0.04). However, the nurse who was not in the clinic and did not have access to medical records spent only 6 min/month/patient focusing on BG results while at the same time providing general educational information. The extremely brief nature of the intervention doubtless accounts for the disappointing results in terms of HbA_{1c} levels, with no difference being seen in the between-groups analysis at 12 months (ΔHbA_{1c} [IG vs. CG] = -0.3%; P = 0.1). Moreover, it seems clear that the method of identifying the most distressed patients was not really efficient.

In France, there has been renewed interest in the telephone consultation system with the Sophia program [19], an assistance program for diabetic patients launched in early 2008 by the French Health Insurance Fund for Employees (Caisse nationale d'assurance maladie des travailleurs salariés [CNAMTS]) in 10 metropolitan regions. The program involves dealing with patients according to their individual risk level, as assessed by the severity of their diabetes complications. Patients considered at low risk were sent information about their disease. Patients at intermediate or high risk, in whom the aim is to reduce the severity of complications and prevent the occurrence of new complications, received telephone calls from trained nurses. Although the evaluation results of the pilot program in a target population of 136,000 diabetic patients have not yet been published, it is already known that these results show no real benefit with regard to HbA_{1c}. Nevertheless, the program has been extended to other areas of France.

Finally, experiments involving low-cost phone consultations have also been conducted with call centers employing non-caregivers. It appears that such interventions may be useful, especially in deprived areas where access to care is limited, and in cases in which metabolic control is not too poor and treatment is relatively straightforward. Benefits in terms of reduction of HbA_{1c} are modest at around 0.4 to 0.5% [20]. However, this kind of intervention has proven to be ineffective in cases of severe blood glucose imbalance, which are frequently related to poor acceptance of diabetes.

What about the internet? Thanks to widespread internet access, very simple systems of communication *via* the web have been tested in Korea. Data (BG values, but also body weight, BP and treatment details) were transmitted to a medical team, which then advised patients *via* the internet. In T2D patients with fairly good metabolic control (n=110, baseline $HbA_{1c}\approx$7.5%), this kind of intervention showed benefits in terms of HbA_{1c} reduction at 3 months (-0.5% in the IG group vs. +0.3% in the CG group, $P<0.001$) [21], which persisted at 30 months [22]. However, these patients were fairly compliant regarding baseline HbA_{1c} and patients with more severe glucose imbalance were not assessed. Furthermore, it is

likely that the time spent by team members reviewing all the data and providing patients with advice or recommendations was consistent, as they also had to answer questions from patients *via* the internet (on average 14 questions per patient in the IG). Conversely, a recent study has been published of an automated clinical-decision support system (CDSS) for T2D patients with no direct involvement of healthcare professionals to manage BG values [23]. Glucometer data are transmitted by landline through a public switched telephone network (PSTN) and the CDSS engine automatically generates instructions tailored to each patient in response to their BG results and these appear directly on the screen of their mobile phone. A diabetes management team including diabetologists, nurses, dieticians and exercise trainers organized and directed patient education. In the intervention group, education was provided to help patients use the system and interpret messages correctly. On testing in a population of 144 T2D obese patients aged >60 years, the reduction in HbA_{1c} was 0.4% in the intervention group (n=49; HbA_{1c} from 7.8 to 7.4%, P<0.001) vs. 0.1% in the control group (n=48; HbA_{1c} from 7.9 to 7.8%, P<0.05), with an intermediate result in the SMBG group. However, the system only allows small adjustments (lifestyle changes or a small increase in insulin dosage: ± 2 insulin units), which explains the modest gain in terms of HbA_{1c} for a relatively sophisticated system.

4. Systems incorporating a cellular phone show more promise

Systems connecting a cellular phone with internet appear much more promising thanks to the handiness of cellular phones and their ability to communicate data in real time.

In the WellDoc™ system, BG values were transmitted *via* Bluetooth from a blood glucose meter to a mobile phone, and then from the mobile phone to a remote server; automated messages were immediately generated by comparison of the value with patient-specific target levels. When patients' blood glucose levels were above or below their target levels, they received real-time feedback on how to correct them *via* messages on their mobile phone screen. Patients were also prompted to enter other information (e.g. medication dosages and carbohydrate intake at meals). All suggested changes to patients' therapeutic regimes were communicated to their HCP. Also, each patient's logbook was sent electronically to the HCP every 4 weeks, or more frequently if necessary. Patients' data were analyzed by automated algorithms and by the research team.

In the 3-month US pilot study reported by Quinn et al. [24], 30 T2DM patients were randomized to an IG (n=15), which received a cell-phone system connected to the internet, or to a CG (n=15), which simply received the standard care. The average decrease in HbA_{1c} for IG patients was -2.03% vs. -0.68% in the CG (P<0.02), although baseline HbA_{1c} levels were high in both groups (9.51% and 9.05%, respectively). In the IG, physicians were four times more likely to titrate/add drugs than in the CG. From the patient's point of view, immediate feedback and the ability to receive advice from a nurse regarding treatment adjustments based on blood glucose results was greatly appreciated. The HCPs, meanwhile, reported that the system facilitated treatment decisions, provided organized data, and reduced logbook-review time. A cluster-randomized clinical trial including three treatment groups (a tiered IG and a CG) has also been conducted using the WellDoc system [25]. Twenty-six primary care practices were randomized to either the control group receiving usual care (UC: providers were asked to care for patients in the usual way) or to one of the three treatment groups: 1) *Coach-only* (CO: a mobile diabetes management software application); 2) *Coach Primary Care Provider (PCP) portal (CPP)*, the latter consisting of a secure messaging center; 3) *Coach PCP portal with decisional support* (*CPDS*); 163 T2 diabetic patients with HbA_{1c}≥7.5% within 3 months of the study start were included (mean HbA_{1c}= 9.4% at baseline). The mean reduction in HbA_{1c} was 1.9% (95% CI 1.5-2.3) in the maximal treatment group and 0.7% (95% CI 0.3-1.1) in the UC group, with a difference of 1.2% (p<0.001) over 12 months. Furthermore the CPDS patients had a significantly greater decrease in mean HA_{1c} than the UC patients for all follow-up times. Even with stratified analysis of HbA_{1c} at baseline (HbA_{1c}<9% or ≥9%), a greater reduction was found in the CPDS group than in the UC group. However, any suggested change in a patient's treatment had to be validated by the HCP and patients could act directly on their BG value; this study did not collect person-specific data on dietary, physical activity and pharmacological management adjustments made for individual patients, and no profiling of patients is possible.

In the field of smart-phones, a version of the Diabeo system has been customized specifically for T2DM patients. This system, the result of collaboration between CERITD and Voluntis, is geared towards patients inadequately controlled by OADs and in whom the introduction of a basal insulin injection at bedtime is warranted. To overcome inadequate titration of basal insulin, the Diabeo system was adapted to provide automated proposals for insulin dose based on an algorithm preset by the physician. However, its chief value remains educational coaching to provide patients with advice on diet and physical activity by way of automatic messages if the results of postprandial blood glucose values or blood glucose values at the end of the afternoon fall outside the target range; advice can also be given to patients in the event of hypoglycaemia. This system is currently being evaluated in the multicentre Telediab-2 study [26] (ClinicalTrials.gov Identifier: NCT00937703). However, it should be recalled that in T2DM, although the amount of carbohydrates consumed is a key element of meal glucose excursion, the relationship between both is not necessarily linear, and we can thus already predict that reducing carbohydrate intake at meals will not always be effective in reducing post-prandial BG values [27].

5. Conclusion

To date, most studies of TM conducted in diabetes care have failed to demonstrate any superiority over traditional care. If we consider only the randomized clinical trials for

meta-analyses, the result remains the same [28]. The chief reason is that meta-analyses have brought together studies of variable quality, regardless of methodology, type of diabetes, study populations and type of device. However, certain studies differ considerably from the others and show a clear benefit in favor of TM (Well Doc, Telediab1). In the light of this review, what are the characteristics of an effective TM system?

An easy-to-use hand-held system, like "a pocket doctor", allowing immediate data entry and immediate feedback about problems and/or a reminder for the patient. In short, the solution will always involve a smart-phone.

Automatic transmission of data to caregivers with automatic data analysis, producing "warnings" to avoid overwhelming the caregiver with too much data, which is impossible to analyze properly in practice.

Such a system would promote tele-monitoring in the event of warnings, with personalized tele-consultations performed by an HCP under the responsibility of a physician. Call centers with non-healthcare providers are of only limited use in this context. Delegation of tasks from the physician to nurses should allow optimization of healthcare by ensuring that caregivers focus on the most distressed patients.

What role could social networks play in this context? Social networks like Facebook or Twitter could help provide education and motivational support by allowing a group of patients to interact with each other and with a caregiver. Such networks could also be involved in supporting a therapeutic solution with proven efficacy. Used together with software designed to manage insulin therapy, this approach could allow immediate, easy and convivial communication with the HCP [29]. However, there may be concerns regarding the lack of confidentiality of the system.

In the specific context of this article, improvements in existing technology and the design of new studies should focus on the question "What new use of electronics and communication technologies will enable patients to improve their blood glucose values by themselves?" This approach should increasingly favor empowerment of patients with respect to diabetes. The first major development is a blood glucose meter directly connected to the data analysis software and to the data transmission system so that patients need not manually enter their blood glucose values. The future thus belongs to glucose meters "plugged" into a smartphone, onto which the telemedicine software would be loaded.

In the case of type-2 diabetes patients treated by dietary measures and oral agents, what are the BG values that can be immediately corrected? Patients can have only a small effect on fasting BG values unless they are treated with basal insulin, in which case an embedded software program can help them adjust their basal insulin doses. Otherwise, they can easily act on moderately elevated blood glucose levels in the late morning or in the late afternoon by means of exercise during both periods; a personalized coaching program enabled by elevated BG values should help them increase their physical activity. The same is true of high postprandial BG values: patients can at least partly reduce some of their postprandial blood glucose levels on their own by reducing carbohydrate load during meals. Simple and customized coaching software packages activated by elevated postprandial BG values are currently being evaluated (Telediab2). However, more elaborate systems of coaching based on dietary self-assessment could be of value here.

For patients with type 1 diabetes, the key objective is proper determination of the correct dose of insulin at any given time. Techniques devoted to functional insulin therapy require accurate CHO counting at each meal. The addition to existing systems such as DIABEO of a program with a support system for immediate determination of carbohydrate amounts should prove valuable. The same is true of patient quantification of physical activity, which is obviously very basic for now, i.e. "moderate", "intensive" and in some cases "intensive" and "prolonged" physical activity. The potentially significant contribution of accurate and miniaturized accelerometers connected to decision support systems for insulin dose determination has still to be considered. Finally, the main reason for the modest (≈0.5%) improvement in HbA_{1c} in most studies assessing continuous glucose monitoring systems (CGMS) is that it is practically impossible, even for a well-trained patient, to properly interpret unaided the 288 blood-glucose values provided daily by the device and to anticipate any changes required in insulin dose, especially for patients on pump therapy. Future developments in this area should clearly focus on software that provides accurate and reliable indications for insulin dose adjustments and then transmits these indications directly to the pump, ultimately leading to an artificial pancreas system.

Conflicts of interest statement

S. Franc and certain of the authors of the manuscript work for CERITD, which has jointly developed the Diabeo system.

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What do patients with diabetes and diabetologists – especially those in private practice – expect from the new technologies for diabetes care in the future?

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Abstract

Thanks to the high volume of patients'consultations delivered, and especially in private practice, diabetologists are able to accurately describe the expectations of diabetic patients with the new and mostly future technologies. In addition, diabetologists are also able to imagine how these technologies will change their medical practices in future.

Keywords: *Diabetes; Diabetes care; Private practice; New technologies; Review*

Résumé

Qu'attendent le patient diabétique et le diabétologue en particulier libéral de la technique appliquée au diabète pour demain ?

Le rythme des consultations permet au diabétologue libéral de transcrire ici quelques attentes des patients diabétiques en matière de technologies nouvelles et futures. Il imagine par ailleurs comment ces nouvelles technologies peuvent modifier sa pratique médicale.

Mots clés : Diabète ; Exercice libéral ; Nouvelles technologies ; Revue générale

1. Introduction

Diabetologists in private practice are able to follow their patients with diabetes throughout the course of their lives. During a consultation, the diabetes specialist has to answer various questions, depending on the age of the patient. However, the recurrent question that ends each visit is invariably the same: What's new in diabetes care?

2. What does a patient with diabetes expect from new technologies for diabetes care in the future?

The answer depends on how the patient sees the technology that is already currently available. When nothing new has been attempted, the expectation is often general, such as "I wish there were something that could keep my blood sugar under control without my having to do anything". In contrast, patients who already use the newer technologies tend to focus on more specific targets according to their own experience. Usually, a patient uses new technologies for a medical reason: to improve glucose control. The benefits for quality of life often appear later with long-term use on a daily basis.

As for insulin infusions, patients expect a more discreet and easy-to-use system. In fact, they usually wish for a pump that is virtually invisible, with no tubes, but with the possibility of acting separately on the reservoir, battery or infusion set. The second most frequent patient's wish is to have the method simplified, with prefilled reservoirs, automatic cannula insertion and filling, and a pump menu available on everyday items such as mobile (cell) phones (smartphones that allow intuitive and easy pump menu control). Indeed, patients expect a system that is friendly, discreet and helpful in their daily life instead of being just a medical device.

But the greatest expectations are naturally related to continuous blood glucose monitoring (CGM) devices. However, patients' wishes often remain vague, as only a few have had the

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opportunity to use the currently available devices. The latter patients are the ones who are best able to clearly express what they are waiting for. Most are expecting a minimally sized, long-lasting device. Patients with diabetes look forward to "closing the loop" with a device that will automatically infuse insulin according to their CGM values. This constitutes the most logical and complex expectation. Yet, most patients do not want a continuously active device, as they wish to keep control of their diabetes. What they do want is a reliable device that they can depend on when they want to. This would allow them to sometimes simply forget that they have diabetes (and let a trustworthy device take control) and, at other times, get help when blood glucose variations are so unpredictable that they just feel like giving up.

Of course, patients' expectations also vary depending on their age and how comfortable they are with the newer technologies: the fear of not being able to control a device can interfere with the patients' attitudes and expectations.

3. What does a diabetologists – especially one in private practice – expect from the new technologies for diabetes care in the future?

The healthcare provider generally has the same opinions and same expectations as does the patient regarding the new technologies for diabetes care, so any of the above-mentioned points may be applicable. However, the diabetologist often has reservations towards any new technology, mainly in terms of reliability and safety, the two mandatory features of any device considered part of everyday medical practice. The diabetes specialist has to consider, beyond the device itself, all of the potential consequences of its wider distribution and use, and how the device is likely to interfere with the patient-physician relationship. Indeed, diabetologists can only hope that new technologies will improve their understanding and analyses of the metabolic state and, thus, help to find adequate solutions. The healthcare provider knows that each step is going to be a personal challenge – and one for the patient as well – provided that the technical aspects are not too complicated. Otherwise, only specialized centres will be able to offer the devices (and education), thereby making the diabetologist in private practice merely a spectator. On the other hand, the diabetologist hopes that the new technologies will be so readily available and so reliable that the current healthcare team can use them routinely in the usual specialized practice setting.

Ultimately, the hope is that all of the new technologies will be both developed and made widely available. Otherwise, the cost of the devices could lead to underestimation of the value of the clinical activities that are the very essence of the profession. Indeed, the use of telemedicine could be part of the relationship, and could be useful for both the patient and healthcare provider if it is recognized and paid for. However, if the development of new technologies presupposes a reduction in the "classical" clinical activities, then two main issues will arise: this could lead to a restriction in human, face-to-face, relationships and a loss of recognition of the profession; and the diabetologist could just become a "healthcare technician" who would only play a role in case of an emergency or device failure, and would only be there to sign prescription forms.

Nevertheless, diabetologists are excited about the arrival of new technologies, as they could be a way of obtaining greater recognition for diabetes care specialists. In addition to their recognized capacities in diabetes education, diabetologists could use the new technologies to improve their abilities and, even more so, their specificity. Hopefully, the new technologies will provide effective solutions and improve the patient-physician relationship.

Thus, by answering enthusiastic patients' questions, but also by encouraging reluctant patients to finally accept modern management approaches to their diabetes, diabetes specialists may hope to see a positive evolution in their everyday practices. This would not be a "futuristic" approach, but an ultimately modern and human-centered one.

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Is continuous glucose monitoring (CGM) for everyone?

To whom should CGM be prescribed and how?

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Abstract

Are all type 1 diabetes (T1DM) patients potential candidates for continuous glucose monitoring (CGM)? Clearly, some patients improve their metabolic control with this tool, such as adults with poor metabolic control, especially those treated with continuous subcutaneous insulin infusion (CSII), and compliant patients with HbA_{1c} levels <7%. There are also less good candidates for CGM, such as patients aged 8-18 years because they are reluctant to wear the sensors or those with new-onset T1DM. Other patient groups have not yet been evaluated, such as patients aged <8 years, women during pregnancy, and those with HbA_{1c} >10% and/or severe hypoglycaemia. Beyond the indications, the mode of use of CGM is crucial. An appropriate patient selection, in order to choose those able to run the tool and motivated to use it, is necessary. How to prescribe the sensors is also an important question. Two approaches have been compared: patient-led and physician-driven prescription. Both modes of using CGM provide similar long-term metabolic improvement. However, physician-driven prescription is probably more cost-effective. The last key question is the education of patients by an experienced team. It can help them to translate the large amount of data from the monitor into effective self-management for optimalizing the CGM experience. However, elaboration of a validated algorithm is necessary to take full advantage of this device.

Keywords: *Type 1 diabetes; CGM; HbA_{1c}, hypoglycaemia; CSII; Screening; Cost-efficiency ratio; Education; Prescription; Sensors; Review*

Résumé

La mesure continue du glucose (MCG) pour tous ? A qui prescrire la MCG et comment ?

Les diabétiques de type 1 (DT1) sont-ils tous des candidats potentiels pour une MCG ? Certains le sont notamment les patients avec une HbA_{1c} > 8 % surtout s'ils sont traités par pompe à insuline et ceux particulièrement compliants avec une HbA_{1c} < 7 %. Certains sont de moins bon candidats: les sujets âgés de moins de 18 ans parce qu'ils sont réticents à porter l'appareil et les diabétiques de type 1 récents. D'autres n'ont pas été suffisamment évalués en particulier ceux âgés de moins de 8 ans, les femmes en cours de grossesse, ceux très déséquilibrés avec une HbA_{1c} > 10 % ou avec hypoglycémies sévères. Au-delà de l'indication, la question de la modalité d'utilisation de la MCG est cruciale. Une sélection des patients appropriées, permettant de choisir ceux qui sont capables de comprendre l'outil et motivés pour l'utiliser, est nécessaire. La modalité de prescription des capteurs est également une question importante. Deux approches ont été comparées: une utilisation libre par le patient et une prescription limitée, guidée par le médecin. L'amélioration métabolique à long terme est comparable. Toutefois, une prescription limitée est probablement plus rentable. La dernière question clef est l'éducation des patients par une équipe expérimentée. Elle permet d'aider les patients à traduire la grande quantité de données du moniteur en modification de doses d'insuline ou de mode de vie, ce qui permet d'optimiser l'utilisation de la MCG. Toutefois, la validation d'un algorithme d'interprétation de la MCG est nécessaire afin profiter pleinement de ce dispositif.

Mots clés : Diabète de type 1 ; MCG; HbA_{1c}, hypoglycémies ; Pompe à insuline ; Sélection ; Rapport cout-efficacité ; Éducation ; Prescription ; Capteurs ; Revue générale.

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1. Introduction

The availability of devices for real-time continuous glucose monitoring (CGM) has aroused considerable interest among patients and physicians who expect potential benefits to blood glucose control from their use. Indeed, several randomized controlled studies have demonstrated that using CGM can improve HbA_{1c} levels and/or the number of hypoglycaemic events in type 1 diabetes (T1DM) patients [1-3]. But are all T1DM patients potential candidates for CGM? In an ideal world where sensors are less costly, why not? Recent evidence from a clinical trial population showed that CGM was cost-effective in the T1DM patients who met the clinical-trial inclusion/exclusion criteria [4]. However, sensors are expensive, and it is neither reasonable nor desirable to ask the government to reimburse all sensors for all T1DM patients. This raises the question of to whom and how to prescribe CGM to provide the best cost-benefit ratio. The answer is still not clear. However, some studies have provided some data, in particular, the French multicentre EVADIAC (*Evaluation dans le Diabète des Implants Actifs;* Evaluation of Active Implants in Diabetics) Sensor Study (publication in progress) [5], which demonstrates that the 1-year use of CGM is able to improve both HbA_{1c} and glycaemic stability in patients with uncontrolled T1DM (Fig. 1).

2. To whom should CGM be prescribed: Who to focus on and who to avoid

All T1DM patients could not potentially improve their metabolic status thanks to CGM. Some of these patients make particularly good candidates: those who have HbA_{1c} levels of at least 7.0% and have demonstrated that they can use these devices on a nearly daily basis [6]; those who have HbA_{1c} levels < 7.0% and have demonstrated that they can also use these devices on a nearly daily basis [6]; patients treated by continuous subcutaneous insulin infusion (CSII). In the EVADIAC Sensor Study, patients treated by CSII (50% of the randomized population) tended to show greater improvements than those treated by multiple daily insulin injections (MDI) [5]. This result is in line with the fact that, when using CSII, patients can more easily make online adjustments to the delivery of insulin according CGM data. Finally, patients who practice frequent daily blood glucometer testing are also good candidates for CGM [8].

On the other hand, some patients are less good candidates. In new-onset T1DM patients using CGM, glycaemic control did not differ from that of patients performing self-monitoring of blood glucose (SMBG), as shown in the paediatric ONSET study [7]. In the 6-month JDRF study, in comparison with adults patients, CGM was less effective in HbA1c reduction in patients aged 8-17 years. This disappointed result was associated with much less frequent use of the devices [2]. However, Subjects in that study who wore the CGM device 6-7 d/wk lowered HbA1c levels by 0.8% without increasing the frequency of low sensor glucose [8].

Some subpopulations have not yet been evaluated, including patients < 8 years, women before and during pregnancy, and those with poor metabolic control (HbA_{1c} > 10%) and/or severe hypoglycaemia. However, one observational study, carried out after the JDRF study, reported a decrease in severe hypoglycaemia in T1DM patients using CGM [9].

So, before prescribing CGM, it is crucial to choose the most appropriate patients. However, the selection criteria is still hypothetical. Are there truly good and bad candidates for CGM? The issue remains moot. For this reason, a test period is needed to confirm the capability and motivation of the selected patients.

3. The screening period

More frequent CGM use is associated with a greater reduction in HbA_{1c}, a finding pertinent to all age groups [2, 8], although not everyone is able to maintain such compliance. In addition, while it provides a lot of information on glycaemic control, CGM can also interfere with daily life. The instrument can sound an alarm in cases of hypoglycaemia or hyperglycaemia. SMBG must be performed,

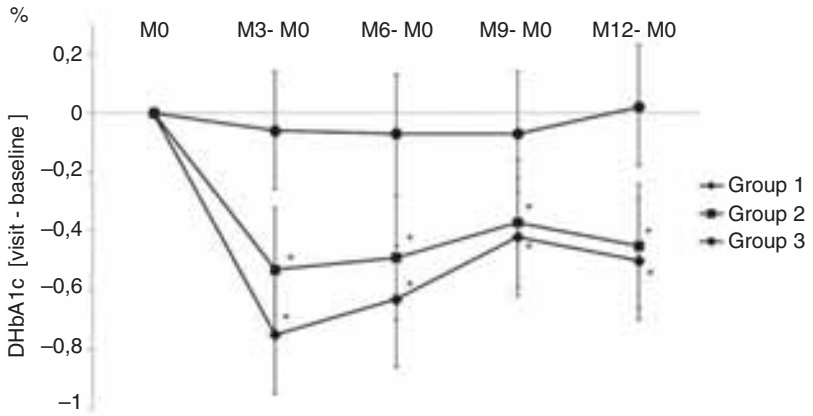

Fig. 1. Results of the EVADIAC Sensor Study: HbA1c change from baseline to 3, 6, 9 and 12 months in three groups: group 1= patient-led prescription of sensors; group 2 = physician-driven prescription of sensors, group 3 = control group (no CGM, SMBG). Values are means (CI 95%). Asterisks denote $P < 0.05$ for comparisons between the two experimental groups and the control group at each time point.

at least for calibration of the device. Patients who are expecting CGM to "nurse" their diabetes in their stead are not good candidates. In the EVADIAC Sensor Study, before randomization, all patients had to wear a CGM device during a 10-day test period [5]. At the end of this period, several points were checked, such as the patients' ability to change sensors, their skill in using the monitor, their willingness to wear the device continuously and, above all, their motivation. Altogether, 257 T1DM patients were screened for inclusion in the study. After the 10-day test period with CGM, 197 patients were randomized into the study. In comparison to the randomized population, patients who failed the screening test (n = 60) were younger, had a shorter duration of diabetes, made fewer daily home glucometer readings, experienced more ketoacidosis events and had attained a lower level of education (Table 1). These results suggest that there is a specific motivated population that is able to use CGM. A test period is essential before beginning a long-term CGM experience to select this subpopulation, whatever the indication and age of the patients.

4. How to prescribe sensors: Patient-led or physician-driven prescription?

How to optimalize the prescription of sensors is a key question. Should it be unrestricted, such as with strips for SMBG, or discontinuously according to the given patient's needs? The EVADIAC Sensor Study was designed to compare two approaches of sensor prescription: patient's self-management *vs* physician-prescribed use of sensors [5]. In the former approach (group 1), patients were advised to use CGM continuously throughout the study. In the latter approach (group 2), the CGM device was prescribed by the patient's physician, who asked the patient to use the sensor intermittently according to guidelines based on glucose outcomes. All patients of this group standed with a 15-day sensor use per month for the first 3 months and, thereafter, they continued either in the same manner or with a more extended use during the following 3 months if, at any visit, the patient presented with at least one of the following criteria: $HbA_{1c} \geq 7.5\%$, or more than four mild hypoglycaemic episodes per week or at least one severe hypoglycaemic episode. Thus, the use of the sensors

Table 1
Comparison of the population that failed the screening test and the patients randomized into the EVADIAC Sensor Study [5].

	Randomized patients (n = 178)	**Screen-failure population (n = 60)**
Male patients (n, %)	95 (53.4)	33 (55.0)
Age (years)	36.4 ± 13.6	31.2 ± 12.3‡
Age < 18 years (n, %)	24 (13.5)	9 (15.0)
Body mass index (kg/m²)[a]	24.7 ± 3.6	23.8 ± 4.2
Duration of diabetes (years)	16.9 ± 9.6	13.2 ± 8.2‡
Insulin regimen (n, %)		
CSII	93 (52.5)	26 (43)
MDI	84 (47.5)	34 (57)
HbA_{1c} (%)	9.0 ± 0.9	9.3 ± 1.3
Patients with one or more episodes of severe hypoglycaemia (n, %)[b]	25 (14.0)	6 (10.0)
Patients with ≥ one diabetic ketoacidosis during the previous year (n, %)	2 (1.1)	4 (6.7)‡
Daily home glucometer readings (n/week)	28.2 ± 14.7	23.8 ± 13.0‡
Educational level		
No diploma (%)	27.1	37.9
College graduate (%)	20.0	27.6
Higher education (%)	52.9	34.5

Values are means ± SD, unless otherwise specified;
‡$P < 0.05$ (randomized *vs* screen-failure population);
CSII: continuous subcutaneous insulin infusion; MDI: multiple daily insulin injection;
[a]body weight in kilogrammes divided by the square of the height in meters;
[b]during the previous year; a severe episode of hypoglycaemia was defined as an event requiring the assistance of another person;

was gradually extended every 3 months to cover 20, 25 and, eventually, 30 days per month.

After 1 year, the HbA_{1c} decrease was similar with both types of prescription, and was significantly greater than that of the control group (Fig. 1). However, it was also observed that the total consumption of sensors over 1 year was significantly lower (by 34%) with the physician-driven *vs* patient-led prescription [median (Q1; Q3) consumption: patient-led prescription, 3.42 sensors/month (2.20-3.91) *vs* physician-driven prescription, 2.25 sensors/month (1.27-2.99); $P = 0.001$]. Thus, the physician-driven prescription was as effective as patient-led prescription, but was evidently more cost-effective, thereby suggesting that physicians should prescribe sensors discontinuously according to the individual patient's needs and preferences.

5. On the necessity to educate patients

As CGM provides 288 glucose measurements every day, it is difficult to analyze all these data, especially in unstable T1DM patients. Most patients only analyze real-time glucose measurements to compensate for hyperglycaemia or hypoglycaemia. During the EVADIAC Sensor Study, patients received specific education by the medical team on how to retrospectively analyze and apply the CGM data, and how to confirm glucose values using the meter included in the Navigator® device before making any therapeutic decisions. The patients' skills were assessed quarterly during the study through a short questionnaire made up of six questions (Table 2). The education was considered optimal if the six items were answered positively at each visit during the entire study and non-optimal if at least one item of the six was not answered positively at any visit. The "optimally educated" patients showed greater improvement in HbA_{1c} compared with the others, a difference that was still significant after adjusting for compliance with CGM (Table 3). Thus, structured education delivered by an experienced team to help patients translate the CGM technology into effective self-management is essential, as suggested by other studies as well [10,11]. However, as yet, there is no validated algorithm, and the analysis of CGM data remains complex.

Table 2
Evaluation of patients' education on how to retrospectively analyze and apply CGM data: The six points checked by physicians at each consultation throughout the EVADIAC Sensor Study [5].

Is the patient able to:
(1) identify fasting and pre-meal glucose levels?
(2) interpret the glucose results and adapt the insulin doses?
(3) identify post-meal glucose levels?
(4) interpret the glucose results and adapt the insulin doses?
(5) identify low glucose levels during the night?
(6) interpret nocturnal glucose levels and adapt basal insulin doses?

Table 3
HbA_{1c} levels decreased according to the patients' education on how to retrospectively analyze and apply CGM data.

Education	Optimal education[1]	Non-optimal education[2]
Patients (n, %)	40/84 (47.6)[3]	44/84 (52.4)[4]
ΔHbA_{1c} (month 12–month 0)	-0.71 ± 0.81	-0.30 ± 0.81
P	= 0.033 (after adjusting for compliance with CGM)	

[1]correct answers to all six items on questionnaire;
[2]at least one incorrect answer to six items on questionnaire;
[3]day 0–month 12: 6 items * four visits = all items correct during the whole study;
[4]day 0–month 12: 6 items * 4 visits = at least one incorrect item during the whole study.

6. Conclusion: It is necessary to help both patients and physicians interpret CGM data

CGM can improve both HbA_{1c} and glycaemic stability in the long term in uncontrolled T1DM patients and in those with HbA_{1c} levels < 7% [6]. However, to achieve such benefits, an initial screening test period of patients to identify those willing to wear the device is important. Furthermore, specific education by an experienced team to enable patients to adapt insulin doses according to CGM data appears to also be invaluable. Nevertheless, despite these conditions, metabolic results may remain suboptimal [12, 13]. One reason is that patients and perhaps even physicians, as well educated as they may be, are not always able to optimalize the use of 288 blood glucose readings per day. Thus, the most important question is not "Is CGM for everyone?", but rather "How can the use of CGM be optimalized?"

The challenge is therefore to elaborate an algorithm that can help patients to determine which CGM data to look at and what decisions to make from these data to take full advantage of the device. Nevertheless, this will never be as effective as an artificial pancreas.

Conflicts of interest statement

J.-P. Riveline participates in advisory boards or as a consultant for Abbott Diabetes Care and has received honoraria, payment for presentations, travel and accommodation expenses covered or reimbursed by Abbott Diabetes Care.

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Advances in pump technology: insulin patch pumps, combined pumps and glucose sensors, and implanted pumps

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Abstract

This review discusses the most recent developments in insulin pump technology. The benefits of the insulin pump to patients with type 1 diabetes are recognized both for its metabolic effectiveness and its positive effects on quality of life. The current pumps are reliable, small and light, and are becoming more and more sophisticated. Nevertheless, there remain practical and psychological constraints for the patient. However, recent patch-pump advances should simplify the technical aspects of pump treatment and enhance patient comfort. Another advance combines the insulin pump with a glucose sensor. Such a combination is logical for optimizing pump use and, to that end, developing an automated or 'closed-loop'system that permits the delivery of subcutaneous insulin adjusted according to measured levels of subcutaneous glucose. Finally, implanted insulin pumps have proven their worth not only because of their simple use, but also for their contribution in the artificial pancreas project. Indeed, the prompt response with intraperitoneal administration of insulin makes it of interest for use in a closed-loop system.

Keywords: *Insulin patch pump; Coupled sensor pump; Implanted insulin pump; Review*

Résumé

Regard prospectif sur la technologie des pompes à insuline : pompes-patch, pompes couplées aux capteurs de glucose, pompes implantées

Cette revue présente les développements récents et en perspective de la technologie des pompes à insuline. Les avantages de la pompe à insuline chez les patients diabétiques de type 1 sont reconnus que ce soit pour son efficacité métabolique ou pour son bénéfice sur la qualité de vie. Les pompes actuelles sont fiables, petites et légères et de plus en plus sophistiquées. Il persiste néanmoins pour le patient des contraintes pratiques et psychologiques. Les avancées récentes visent à développer des pompes patch qui devraient simplifier l'aspect technique du traitement et améliorer le confort des patients. Une autre avancée concerne le couple pompe à insuline-capteur de glucose, combinaison logique pour optimiser l'utilisation de la pompe avec en perspective l'élaboration d'un système automatisé ou « boucle fermée » permettant une délivrance d'insuline sous-cutanée ajustée à la mesure sous-cutanée du glucose. Enfin les pompes à insuline implantées ont fait leurs preuves dans leur utilisation simple mais aussi dans un projet de pancréas artificiel. En effet, l'administration intrapéritonéale de l'insuline a une grande réactivité, intéressante pour son utilisation dans un système de boucle fermée.

Mots clés : Pompe-patch ; Pompe couplée à un capteur de glucose ; Pompe implantée ; Revue générale

1. Introduction

In patients with type 1 diabetes, the benefits to glycaemic control and quality of life of external insulin pumps have been clearly established [1]. The main indications for an external pump include persistently elevated HbA_{1c} despite intensive multiple-injection insulin therapy, repeated hypoglycaemia and significant glycaemic variability [2]. Other medical circumstances may also warrant pump treatment, such as pregnancy and type 2 diabetes that has failed to respond to intensified multiple-injection insulin therapy. Specific paediatric indications may also be seen in certain cases [2].

Today's insulin pumps are the result of decades of design and engineering efforts towards the development of reliable, secure and user-friendly modern pumps. These pumps are small and light, and offer technical solutions that are suited to diabetic patients' needs. Their integrated software has also evolved, and can now keep track of the delivered insulin and blood glucose measurements, enable bolus calculation and permit link-ups with other compatible systems.

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The most recent pump-technology research concerns the development of insulin patch pumps and pumps coupled with glucose sensors. The present review examines their basic concepts and describes only those devices already available or under development, and reports, if need be, the results of clinical studies. The technology of the implanted insulin pump is included in this review as well.

2. Insulin patch pumps

Although the benefits of external pump treatment have been clearly established, the treatment modality nonetheless requires strong patient motivation and involvement. However, certain features of the external pump could be improved to reduce treatment constraints and improve patients' quality of life. Indeed, the initial technical education on how to use the pump and insert the catheter takes time, some patients have the impression of being attached to an external object; equipment problems, such as catheter occlusion and bent cannulae, are common occurrences, disconnecting the pump is recommended before taking a shower, or engaging in water or other sports activities.

Recent technological progress has resulted in the development of "insulin patch pumps" that ought to simplify the technical aspects of treatment and improve patient comfort [3,4]. The term "patch", however, may be a misnomer. Although these new pumps are smaller and free of tubes, they often have subcutaneous cannulae through which insulin is injected. The patch pump is nevertheless an innovative system in the field of insulin pumps. The concept comprises an insulin reservoir, delivery system and cannula, all of which are integrated into a small, wearable, disposable or semi-disposable device. The patch pump combines the functions of a conventional insulin pump with the following advantages: by eliminating the tubing, it is easy to use; to initiate pumping requires only simplified training; and it is discreet.

The development of the patch pump has been initiated by a large number companies ranging from start-ups to established firms. At present, a few of these pumps have been approved for marketing in the US by the Food and Drug Administration (FDA), while a wide range of other devices is also reported to be currently under development [5].

2.1. Currently available insulin patch pumps

Only the OmniPod® (Insulet Corp., Bedford, MA, USA) (Fig. 1) is currently available for use, and has been sold in the US for several years [5]. The device, distributed by Ypsomed, will soon be available in France. The pump/reservoir unit (Pod) is a tube-free disposable device applied to the body with adhesive, and changed every 3 days. The Pod has an integrated infusion set and automated inserter, and communicates wirelessly with the personal data manager (PDM), a separate controller device that manages insulin delivery. In addition, the PDM contains an integrated blood glucose meter and food database, and is waterproof, allowing it to be worn during showering or swimming. In one short-term study [6], type 1 diabetic patients preferred using the Pod to their conventional pump. Another prospective study [7] demonstrated the safety and efficacy of 500 U of insulin delivered by OmniPod in type 2 diabetes insulin-resistant patients.

Fig. 1. The OmniPod® insulin patch pump comprises a personal data manager (PDM, left) and a tubeless pump/reservoir unit (Pod; right).

2.2. Approved insulin patch pumps not yet available

Two patch pumps have been approved by the FDA, but are not yet on the market [5]. The Solo™ MicroPump Insulin Delivery System (Medingo US, Inc., Tampa, FL, USA) (Fig. 2) has two parts: the micropump itself; and a remote device that programmes and directs the micropump. The micropump is small and slim, and consists of a 2 mL insulin reservoir, a cannula cradle infusion set and a pump base. The disposable insulin reservoir and cannula must be replaced every 2 to 3 days. The pump base includes a reusable 90-day unit that holds the electronics, memory, pump motor and bolus buttons. The base must be clicked out of the cradle before swimming or engaging in contact sports. Boluses are delivered *via* the remote device or directly from the pump.

The Finesse™ patch pen (Calibra Medical, Inc., Redwood City, CA, USA) is a disposable and completely manual system that only delivers insulin boluses. As there are no electronics, the bolus is delivered by depressing bolus-release buttons.

2.3. Insulin patch pumps under development

There are numerous patch pumps currently being developed [5]. The Cellnovo™ pump (Cellnovo Ltd, London, United Kingdom) is a minipump that is programmable *via* a mobile handset based on the principles of Apple technology; it consists of a controller for the insulin pump and a blood glucose meter, and also contains a food library. The handset transmits data to a centralized server. The minipump's insulin reservoir has a capacity of either 0.5 ml or 1.5 ml, and is connected to a cannula and minitubing, each of which needs to be replaced every 3 days. The pump battery is rechargeable.

Fig. 2. The Solo™ MicroPump Insulin Delivery System has two parts: the micropump itself (left), and a programmable remote device (right).

The V-Go™ pump (Valeritas, Inc., Bridgewater, NJ, USA) is a fully disposable transdermal device with a preset basal rate and on-demand bolus delivery. The device needs to be replaced daily. It has no programming, no electronics and no batteries.

The JewelPUMP™ (Debiotech SA, Lausanne and STMicroelectronics, Geneva, Switzerland) is based on the MEMS Nanopump™ technology and comprises two parts: the reusable part contains the electronics and includes remote communication for distant programming; the other, disposable part includes a reservoir, pumping mechanism and batteries. The insulin reservoir is refilled every 6 days.

The CeQur™ pump (Montreux, Switzerland) is intended for type 2 diabetes patients. The pump delivers a constant basal rate and on-demand bolus delivery at the push of a button.

The PassPort™ Transdermal System (Altea Therapeutics Corp., Atlanta, GA, USA), currently under phase-I clinical evaluation, dispenses only a basal rate of insulin. The system includes an applicator and a PassPort™ Patch, which contains a reservoir and a tiny metallic filament screen known as the "porator". The applicator delivers an electrical charge to the porator, thereby galvanizing the filaments and scattering the closest skin cells. Micropores are thus created on the surface of the skin, permitting transdermal passage of insulin. The delivery method can be configured to achieve either systemic or localized action of the therapeutic agent. The aqueous micropores allow the rapid and sustained flow not only of insulin, but also of proteins, peptides, carbohydrates and small molecules into the body without the use of needles or pumps.

The NiliPatch Disposable Insulin Pump System (NiliMEDIX Ltd, Tirat-Carmel, Israel) delivers basal and bolus insulin. The pump uses a pressure-triggered release mechanism, and is controlled by a system of valves and sensors. The NiliPatch pump has been certified for marketing in the European Union and Israel.

The Freehand™ system (Medsolve Technologies, Inc., Manhattan Beach, CA, USA) is a remote-controlled basal and bolus insulin-delivery pump system with a 3-month lifetime. The system offers seven basal profiles. Basal delivery can be temporarily suspended, and boluses can be delivered either remotely or manually.

Little information is available at this time on the following models supposedly under development: the Medipacs patch pump (Medipacs, Inc., San Diego, CA, USA); the Medtronic patch delivery system (Medtronic, Inc., Minneapolis, MN, USA) and the SteadyMed patch pump (SteadyMed Ltd, Tel-Aviv, Israel).

In summary, there are many patch pumps at various stages of development, but few are currently on the market or anticipated to soon be on the market. The very concept of a patch pump will improve patient comfort and eventually improve patient compliance with treatment. Moreover, it should reduce barriers to pump acceptance, particularly in type 2 diabetic patients.

3. Insulin pumps coupled with glucose sensors

The combined use of real-time continuous glucose monitoring (RT-CGM) and continuous subcutaneous insulin infusion (CSII) *via* an external pump is a logical development with a view towards an artificial pancreas for the optimal treatment of type 1 diabetes. The goal is to implement an automated system or "closed loop" that permits the delivery of subcutaneous insulin adjusted to measured levels of subcutaneous glucose.

3.1. Non-automated coupling of insulin pumps and glucose sensors

While awaiting the development of an artificial pancreas, a preliminary step is the non-automated coupling of an insulin pump to a glucose sensor. The combined use of both systems appears consistent with the conceptual plan to optimalize use of the pump. The patient can continuously adjust the delivery of insulin based on the values and trends indicated by real-time data from the glucose sensor. This is an example of an "open-loop" device: the patient can maintain glucose control by interpreting the data from RT-CGM, and use it to modulate insulin basal rate, temporarily stop the pump and/or deliver additional insulin boluses. The theoretical value is such

that systems incorporating insulin pumps and glucose sensors are already available to patients. These sensor-augmented pump devices include a subcutaneous glucose sensor with a 6 to 7 day lifetime that communicates *via* telemetry with an external insulin pump. The pump's screen displays glucose sensor data and emits an audible alarm whenever high or low values are detected. The first such system, sold in 2006, was the MiniMed Paradigm REAL-Time System® (Medtronic, Inc.). Another system soon to appear on the market is the Animas® Vibe™ (Animas Corp., West Chester, PA, USA).

Self-monitoring of blood glucose (SMBG), in its common clinical use, only reports glycaemia levels at a precise point in time, generally before meals and at bedtime. It has been shown that the frequency of SMBG is inversely correlated to the value of HbA_{1c} [8]. In practice, most patients rarely take more than four to six blood glucose measurements per day. On the other hand, even if sustained, the SMBG provides glucose information for only one point in time, with no information on the kinetics of blood glucose and/or its rate of change. For these reasons, RT-CGM from the start appears to have added value when combined with CSII [9]. This added value can be examined in recent randomized studies evaluating the effectiveness of sensor-augmented pumps.

3.1.1. Effectiveness of RT-CGM associated with an insulin pump

All of the studies [10-13], with the exception of the first [10], confirmed the efficacy of RT-CGM associated with an insulin pump in reducing HbA_{1c}, even though the benefit was sometimes observed only in subgroups of patients. The first study [10] involved poorly controlled type 1 diabetic patients already being treated with an insulin pump. These patients were randomized into two groups: the first continued with SMBG and pump therapy; while the second was treated with a sensor-augmented pump (the MiniMed Paradigm REAL-Time System). After 6 months, the HbA_{1c} decrease of about 0.6% to 0.7% was similar in both groups. Although the overall results were negative in terms of added value with RT-CGM, post-hoc analysis highlighted the importance of how long the glucose sensor was worn. Of the patients using the sensor >60% of the time, there was an HbA_{1c} decrease of almost 0.9% during the study. In contrast, the control of diabetes worsened in patients wearing the sensor < 60% of the time, with an HbA_{1c} increase of almost 0.2%.

The French multicentre REAL Trend study [11] took into account this observation of the essential role of compliance with wearing the sensor. The study enrolled poorly controlled type 1 diabetes patients, treated with multiple daily insulin injections (MDI), who were randomized into two groups: the first group began therapy with a pump and conventional SMBG; the second group used a sensor-augmented pump (MiniMed Paradigm REAL-Time System). From the outset, the latter patients were asked to use the glucose sensor >70% of the time. After 6 months, the per-protocol analysis (patients compliant with sensor use) showed that HbA_{1c} values were significantly different between the pump *vs* sensor-augmented pump groups (-0.55% *vs* -0.96%, respectively; $P<0.005$). The study further highlighted the need for a preparatory period of a few days for patients using the glucose sensor. This period enabled the patient to determine whether or not wearing the glucose sensor was tolerable in the medium term.

Unlike the two previous studies in the series, the STAR-3 study [12] lasted 1 year and not only evaluated RT-CGM, but the system combined with a sensor-augmented pump. STAR-3 involved poorly controlled type 1 diabetes patients treated with MDI and randomized into two groups: the first continued MDI treatment with SMBG; the second received sensor-augmented pump treatment (MiniMed Paradigm REAL-Time System). After 3 months and up to the end of the study, HbA_{1c} was significantly improved in the sensor-augmented pump group compared with the MDI group (at 12 months, -0.8% *vs* -0.2%, respectively; $P<0.001$). In addition, the proportion of patients achieving the HbA_{1c} target of <7% was almost three times higher in the sensor-augmented group. Again, compliance with sensor use was crucial for determining metabolic benefits: sensor frequency of use of 61–80% was associated with a reduction in HbA_{1c} of 0.79%, while a use frequency of 81-100% was associated with a reduction of 1.21%. On analyzing the factors predictive of sensor-augmented pump's metabolic benefit [13], the baseline predictors for HbA_{1c} reduction were HbA_{1c} level >9%, patient's age >36 years at randomization and age at the onset of diabetes >17 years.

Thus, the REAL Trend and STAR-3 studies [11,12] clearly demonstrated the metabolic effectiveness of pump therapy optimalized by glucose sensors, and the efficacy may even have been underestimated. The first reason is that the improvement in HbA_{1c} was also observed in the control groups. These improvements may have been linked to intensification of SMBG as well as tight coaching by study investigators. Another reason is that the investigators themselves in the first study may not perhaps have had enough experience with RT-CGM.

The results of the SWITCH study [14], a multicentre randomized, controlled, crossover study, have not yet been reported, but the findings should resolve the question of added value with RT-CGM associated with CSII. Indeed, the study was designed to assess whether CGM provides any additional benefits to patients already being treated with a pump. It was carried out over two experimental periods of 6 months each, separated by a washout period of 4 months. The patients' usual pump was replaced by a pump coupled with a glucose sensor. Patients were then randomized into one of two study arms. In one arm during the first 6 month period, the sensor was set to ON while, in the other arm, the sensor was set to OFF. The settings were then reversed for the second 6 month period.

3.1.2. Pump patients in other studies showing benefits with RT-CGM

The benefits of RT-CGM have been shown in other studies where the mode of insulin therapy was not modified at randomization, and where randomized patients in the glucose-sensor group

followed their previous insulin treatment [15,16]. One multicentre study sponsored by the Juvenile Diabetes Research Foundation (JDRF) [15] included type 1 diabetes patients receiving intensified insulin therapy, two-thirds of which were CSII. This study demonstrated that RT-CGM is effective for reducing HbA_{1c} in patients aged >25 years, but has less effect in younger patients. Yet again, glycaemic control was improved with prolonged and sustained use of the sensor during the 6-month study. There was no difference in efficacy between patients using the pump and those receiving multiple injections of insulin.

More recently, a 1 year multicentre study was conducted by the EVADIAC sensor study group involving poorly controlled type 1 diabetic patients treated with a pump or multiple injections in the same proportions. Patients were randomized into three groups: a control group following the traditional SMBG; and two groups using RT-CGM, one *ad libitum* and the other with a frequency determined by the physician based on metabolic criteria. At 3 months, HbA_{1c} improved significantly in both groups using the RT-CGM compared with the control group and at 1 year, the difference was 0.5%. Several factors were involved in this outcome, including adherence to sensor use, mode of insulin therapy and patients' education. At 1 year, there was a significant HbA_{1c} reduction of 0.67% in pump patients in the RT-CGM groups *vs* the control group. In patients using injections, HbA_{1c} decreased by only 0.28%. This study also highlighted the impact of specific patients' education that enabled them to properly interpret and use the CGM data. In contrast, a 6-month prospective study [17] concluded that CGM provided comparable benefits to metabolic control for patients using either MDI or CSII therapy.

In all these studies but one [10], the HbA_{1c} reduction was not associated with an increase in severe or moderate hypoglycaemia. However, these trials were not designed to study hypoglycaemia, and the patients had not been selected on that basis. On the other hand, a randomized and controlled multicentre trial [18] was specifically designed to evaluate the effect of CGM on hypoglycaemia in type 1 diabetic patients who were well controlled (HbA_{1c}<7.5%) and treated with either an insulin pump or multiple injections. The results of this 6-month study showed significantly reduced time spent in hypoglycaemia in patients who used CGM compared with SMBG, with a concomitant decrease in HbA_{1c}.

In practice, hypoglycaemia is a major limiting factor for good glycaemic control, making the prevention of hypoglycaemia one of the most important benefits anticipated from glucose-sensor pumps.

3.1.3. Automated coupling of insulin pumps and glucose sensors for preventing hypoglycaemia

Hypoglycaemia alerts are integrated into RT-CGM systems. However, the DirectNet Study Group [19] showed that 71% of cases – specifically, children and adolescent patients – did not react to the hypoglycaemia alerts that occurred during sleep. This is important as most episodes of severe hypoglycaemia happen at night [20].

3.1.4. Suspending insulin delivery when hypoglycaemia is predicted

The idea is to use the coupled sensor-pump as a "partially closed loop" to defer the delivery of insulin when hypoglycaemia is predicted. Pilot-study results are encouraging [21-23]. These studies tested the functionality of an algorithm that detects pending hypoglycaemia, and assessed whether hypoglycaemia was prevented by temporary stoppage of the pump. The first study [21] involved 22 type 1 diabetic patients, treated with an insulin pump, who were asked to undergo RT-CGM twice with the FreeStyle Navigator® (Abbott Diabetes Care, Alameda, CA, USA). First, the basal rate of the insulin pump was gradually increased so as to induce hypoglycaemia (<60 mg/dL). Based on the insulin sensitivity noted in this experiment, the basal rate was increased again in a second test to induce a comparable fall in glucose and projected blood glucose of < 60 mg/dL. Data from the FreeStyle Navigator were reported in a database with two algorithms for predicting hypoglycaemia. From these models, the probability of hypoglycaemia was generated to produce an alarm. For each subject, only one of the two algorithms was used in the second test. When the algorithm predicted a future blood glucose of < 80 mg/dL, the insulin pump was stopped for a period of 90 min. With a 30 min prediction, 60% of hypoglycaemias were foreseen and prevented. With a 45 min prediction, 80% of hypoglycaemias were prevented. Hyperglycaemic rebound was not observed after temporarily stopping the pump.

In another study specifically addressing prevention of nocturnal hypoglycaemia [22], the hypoglycaemia-predicting algorithm (HPA) combined five separate algorithms, all based on CGM 1-min data. This HPA algorithm was developed from 21 studies using the FreeStyle Navigator system. The five pump-suspension algorithms were based on a 35 min prediction and used an 80 mg/dL glucose threshold. When two algorithms were used, hypoglycaemia was prevented in 75% of nights and in 84% of cases.

Yet another study [23] assessed the aggressiveness and effectiveness of HPA according to the settings for the following parameters: hypoglycaemia prediction time (35, 45 and 55 min); hypoglycaemia threshold value (70, 80 and 90 mg/dL); and the number of algorithms used (three, four and five). If, with a glucose threshold of 80 mg/dL, three of the five algorithms were used, then 91% of hypoglycaemias were predicted 35 min beforehand. If four algorithms were used, 82% of events were predicted 35-55 min ahead of time. According to individual sensitivities, these settings can differ from day to night, and modulate specificity and reduce the number of false alarms. However, as these clinical studies were conducted at a clinical research centre, real-life studies are now needed.

3.1.5. Suspending insulin delivery when hypoglycaemia is detected

A recent evolution [24] of the Paradigm REAL-Time pump is the Veo™ model (Medtronic), which has been available in

Europe for nearly 2 years. This system uses data transmitted by the glucose sensor to automatically suspend the delivery of insulin in cases of hypoglycaemia. This "automatic stop" ("low-glucose suspend", or LGS, function) is interesting, but is activated only when the sensor detects interstitial glucose levels below a predetermined threshold rather than before the hypoglycaemia occurs. Clinical experience with the Paradigm Veo pump is still limited, and the efficacy of the system in reducing hypoglycaemia has only been evaluated in a few recent short-term studies [25,26]. One study was conducted in type 1 diabetic adults fitted with the Veo pump [25]. Hypoglycaemia events were examined during two consecutive periods. During the initial 2-week period, the automatic stop was not activated (LGS was set on OFF). Following this, during a second period of 3 weeks, the LGS was enabled (set on ON). The results showed that, in patients at high risk of hypoglycaemia, the LGS function significantly reduced nighttime hypoglycaemia duration with no hyperglycaemic rebound or ketosis. Similar results were reported in another study conducted in diabetic children and adolescents [26].

Major progress is expected in the field of glucose-sensing and insulin-delivery technology. As an example, systems could be designed to maintain glucose within the range of normoglycaemia. There would have to be an automatic stop of insulin infusion if glucose falls below a given threshold, and delivery of an insulin bolus if glucose rises above an upper threshold [27].

In summary, in its current application, the coupling of an insulin pump with a glucose sensor is an open-loop system in which the patient has to interpret data from RT-CGM to adapt the delivery of insulin. Unquestionably, studies have shown that combining RT-CGM and CSII rapidly improves glycaemic control in a sustainable manner in type 1 diabetes patients. However, the device works best for motivated patients who are trained in intensive insulin therapy as well as in the interpretation of large amounts of complex CGM data. Nevertheless, the most recent technological progress used in actual clinical practice represents an early version of an artificial pancreas system also known as an "LGS system".

4. Implanted pumps

The use of implanted insulin pumps began enthusiastically a little over 20 years ago. The objective was to free the patient from the constraints of injections as well as to develop the components for an implantable artificial pancreas by taking advantage of the benefits derived from the use of intraperitoneal insulin delivery.

4.1. The intraperitoneal route

Subcutaneous (SC) insulin absorption is slow, variable and induces secondary hyperinsulinaemia. These limitations have led to alternative routes being sought for continuous ambulatory infusion of insulin [28]. Studies in animals have shown the benefits of the intraperitoneal (IP) route, which has pharmacokinetics that are closer to physiological than the SC route [29].

After delivery into the peritoneal cavity, insulin is primarily resorbed in the portal vein. There is an approximately 50% degradation during the first hepatic passage, thereby recreating a physiological insulin gradient between the portal vein and systemic circulation [30]. Compared with the SC route, the IP route induces lower peripheral insulinaemia while allowing resorption and a faster return to baseline plasma levels [31,32]. These insulin kinetics are more physiological [32], maintaining reproducibility of insulin profiles in the long term [33] and resulting in an improved glucagon response to hypoglycaemia [34].

The use of the IP route for type 1 diabetes treatment was made possible by the development of programmable implantable pumps that deliver insulin through an IP catheter. Pilot trials [35-37], conducted in the 1980s, demonstrated the feasibility, efficacy and safety of this therapeutic approach. Insulin therapy *via* an implanted pump began in 1989 with its primary development in France. As a result, the French data are foremost in the world. There are 15 centres in France included in the association EVADIAC (*Evaluation dans le diabète du traitement par implants actifs*; Evaluation of treatment with active implants in diabetes). EVADIAC monitors and gathers information into a computerized central registry.

The current implant, the MIP 2007 model (Medtronic-MiniMed, Northridge, CA, USA), underwent improvements to the electronic and battery components of the previous model. It has been in use since 2000 and has a 7- to 10-year battery life. Insulin delivery options are similar to those of the most up-to-date external pumps, and are programmable through a personal pump communicator (PPC). The catheter is inserted into the peritoneal cavity, while the pump itself is implanted in the abdominal wall. In 2007, the MIP 2007 device and Insuplant® 400 IU/ml (Aventis Pharma, Frankfurt, Germany), a semi-synthetic insulin used in implanted pumps, received marketing approval from the French regulatory agency. However, currently, Insuplant 400 IU/ml has been replaced by Insuman Implantable 400 IU/ml (Aventis Pharma), an ordinary recombinant insulin. As with Insuplant, this new insulin has been stabilized to prevent denaturation and precipitation in the implanted pump reservoir. The AMM is pending.

4.2. Clinical use

Observational clinical studies conducted by EVADIAC have clearly demonstrated the feasibility, metabolic efficacy and safety of the implanted pump in type 1 diabetic patients [38-41]. The metabolic benefits consist of a reduction in HbA_{1c} as well as in the frequency of severe hypoglycaemias and glycaemic variability. These benefits are maintained in the long term even in type 1 diabetics who remain far from the HbA_{1c} target of 7% and/or have large blood glucose fluctuations, including severe recurrent hypoglycaemia, despite tight coaching and intensified education with SC insulin

treatment [42]. A Dutch study [43] also showed that, with an implanted insulin pump, not only was HbA_{1c} significantly improved in those who were previously poorly controlled, but instability-related diabetic hospitalizations were also significantly reduced.

Several randomized clinical trials have compared the IP route with an implanted pump and the SC route with an external pump or multiple injections [44-47]. The most recent study [47] demonstrated significant improvement in glycaemic control, expressed as a 0.8% decrease in HbA_{1c} over a period of 6 months when using implanted insulin pumps compared with SC insulin treatment in 24 poorly controlled diabetic patients.

The complications of treatment with implanted insulin pumps have clearly decreased over time and with user experience. These complications are mainly problems localized to the abdominal implantation site or due to under-delivery of insulin by the pump. Localized site problems dropped from 8 to <2 per 100 patient-years between 1990 and 2000 [41,48]. Usually, this represents localized infection [48,49] requiring temporary removal of the pump. Specific asepsis procedures and prophylactic antibiotics have helped to eliminate nearly all of these complications. Under-delivery of insulin results from either aggregation of insulin in the pump mechanism or obstruction of the peritoneal catheter. Insulin aggregation in the pump was linked to a defect in the Insuplant insulin that was then in use. The phenomenon is reversible in most cases by rinsing the pump with a soda solution. Its incidence has also dropped from 15 to <4 per 100 patient-years [39,41]. Other less common problems include electronic failure and premature battery depletion, which were recently reported to be 0.5 and 2.2, respectively, per 100 patient-years [42]. In addition, a higher rate of anti-insulin antibodies has been reported with implanted pumps, mainly in patients with elevated levels before implantation [50-52]. Many factors can cause this immunogenic response: the formulation of the insulin itself, the peritoneal route or, more likely, insulin aggregates in the pump mechanism have turned out to be highly immunogenic [53,54]. However, elevated levels of anti-insulin antibody have, in most cases, little effect on metabolic control in patients, although they have been described as blunting the plasma free insulin peak after a bolus, which can affect postprandial glycaemic control [55]. On the other hand, extreme cases of "low morning syndrome" [50,51] have been reported due to the disabling combination of late-night hypoglycaemia and postprandial hyperglycaemia.

Nevertheless, compared with the metabolic benefits with implanted pumps in unstable type 1 diabetes patients, the rate of complications appears acceptable. The quality of life in patients treated with implanted pumps was assessed using validated questionnaires in some pilot studies [37,56], and revealed that patient satisfaction had significantly improved on switching from multiple injections or CSII to implanted pump therapy [37]. The impact of diabetes was also found to be significantly less in type 2 diabetic patients treated with implanted pumps [56]. A more recent study [47] reported better health-related quality of life and greater patient satisfaction with implanted pumps compared with SC insulin therapy. In addition to these quality-of-life evaluations, there is also the occasional patient's testimony describing the benefits experienced with an implanted pump [57].

4.3. Indications

The current indications for an implanted pump are related to user experience and the metabolic benefits observed, and were presented in an EVADIAC "position statement" that has since been recently updated [58,59]. Treatment with an implanted insulin pump is indicated for type 1 diabetic patients with an HbA_{1c}>7% and/or presenting with large blood glucose fluctuations, including moderate and/or severe recurrent hypoglycaemic events despite intensified treatment with SC insulin.

4.4. Current use and perspectives

At this time, implanted insulin pump therapy is limited to a minority of selected patients based on who is likely to obtain the most benefit. There are currently 458 diabetic patients with an implantable pump: 370 in France, 3 in Belgium, 63 in the Netherlands and 22 in Sweden. The limitations of this treatment mode are the result of its technically specialized medical requirements, significant cost and reimbursement guidelines, as well as its limited manufacturing. Despite these limitations, however, the benefits provided to patients requiring this form of insulin therapy should be borne in mind.

The need to improve diabetes management to reduce the frequency, severity and consequences of hypoglycaemic events and degenerative complications constitutes a major public-health issue. Considering the health costs generated by the management of diabetes complications (such as hospitalization, work absences, medical transports, dialysis, retinal laser treatment, vascular bypasses and amputations), treatment with an implanted insulin pump should certainly constitute an acceptable cost and remain available when validly indicated.

Moreover, as regards implanted pumps coupled with glucose sensors, the implanted insulin pump is part of an innovative technology for diabetes and an important step towards the development of an artificial pancreas. Indeed, the pharmacokinetic properties [31,32] of IP-administered insulin give it a high reactivity that is of particular interest for use in a closed-loop system. Pilot studies have also shown encouraging results with implanted pumps coupled with intravenous [60] and SC [61] glucose sensors.

Thus, important advances have been made in the technology of insulin pumps, and the research is ongoing. The immediate expected patients' benefits are accurate data, ease of use, and improvements in metabolic control, quality of life and compliance. The benefits to come are related to its implementation as a component of an artificial pancreas.

Conflicts of interest statement

The author has no potential conflict of interest relevant to this article.

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Towards an artificial pancreas at home

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Abstract

Aim – To review the recent clinical research related to the development of an artificial pancreas and the current perspectives for its home use.

Methods – All clinical investigations assessing closed-loop insulin delivery systems in diabetic patients in the literature were collected and analyzed to identify any significant advances as well as bottlenecks.

Results – The development of an artificial pancreas for ambulatory use offering an optimal substitute for insulin secretion has shown promising evolution over the past decade. The accumulated improvements achieved on the performance of insulin pumps using subcutaneous and intraperitoneal routes, continuous glucose monitoring and algorithms driving insulin infusion according to glucose measurement have led to numerous clinical trials recently, albeit only in a hospital setting so far. The key obstacles to achieving permanent normal glucose control are related to the delay of insulin action when infused subcutaneously or, at a lesser extent, into the peritoneal cavity, and blood glucose estimation made by subcutaneous interstitial measurement. These time lags impair the reactivity of the system, and suggest a need to develop complex algorithms aiming at their compensation. So far, manual interventions are needed at times of food intake to prevent hyper- or hypoglycaemic excursions when insulin changes rapidly.

Conclusion – The most recent models using subcutaneous insulin infusion and glucose measurements linked by predictive control algorithms offer sufficient effectiveness and safety to consider their forthcoming use at home, during the night as a first step.

Keywords: *Type 1 diabetes; Insulin; Artificial pancreas; Insulin pump; Continuous glucose monitoring; Review*

Résumé

Vers le pancréas artificiel à la maison

But – Etablir une revue de la recherche clinique récente sur le développement d'un pancréas artificiel et les perspectives actuelles pour une utilisation à la maison.

Méthodes – Les expérimentations cliniques rapportées dédiées à l'évaluation des systèmes de délivrance d'insuline en boucle fermée ont été rassemblées et analysées pour identifier les avancées significatives et les écueils.

Résultats – Le développement d'un pancréas artificiel ambulatoire permettant d'assurer une suppléance optimale de la sécrétion d'insuline a connu une évolution très prometteuse au cours de ces dix dernières années. C'est le cumul des progrès réalisés sur les performances des pompes à insuline utilisant la voie sous-cutanée ou intra-péritonéale, la mesure continue ambulatoire du glucose et les algorithmes de gestion de la perfusion d'insuline selon la mesure du glucose, qui a permis de mener des essais cliniques nombreux au cours de ces dernières années, pour l'instant toujours en milieu hospitalier. La difficulté pour atteindre une normalisation glycémique permanente est due aux retards d'action de l'insuline liés à la perfusion sous-cutanée ou, à un moindre degré, intra-péritonéale, et d'estimation de la glycémie à partir de la mesure du glucose interstitiel sous-cutané. Ces retards qui altèrent la réactivité du système imposent le développement d'algorithmes complexes visant à les compenser. Le recours à une intervention manuelle est pour l'instant toujours nécessaire lors des prises alimentaires pour éviter les échappées hyper- ou hypoglycémiques alors que les besoins en insuline changent rapidement.

Conclusions – Les derniers modèles qui utilisent la perfusion d'insuline et la mesure du glucose sous-cutanées reliées par des algorithmes selon un modèle prédictif permettent d'assurer une efficacité et une sécurité suffisantes pour entrevoir un prochain passage à la maison, en période nocturne dans un premier temps.

Mots clés : Diabète de type 1 ; Insuline ; Pancréas artificial ; Pompe à insuline ; Mesure glycémique en continu ; Revue générale

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1. Introduction

Continuous advances in insulin therapy (insulin analogues, pumps), glucose monitoring (quick measurements from small capillary samples, continuous glucose monitoring) and therapy-related education (functional insulin therapy, telemedicine) have not brought about a final solution to the crucial challenge related to the loss of insulin secretion: to provide permanent coverage of body insulin while maintaining blood glucose levels within the near-normal range. The result is the still uncontrolled risk of complications due to long-term hyperglycaemia, and the constant worry in the insulin-treated diabetic patient over hypoglycaemic events, both of which can lead to serious impairment of health-related quality of life.

Restoration of insulin secretion by pancreas or islet transplantation brings a solution by re-establishing close to physiological blood glucose control for a variable length of time, albeit while bringing other risks [1]. Islet transplantation is associated with a lower interventional risk than pancreas grafts, but allogenic transplants require immune suppression, which is associated with negative short-, middle- and long-term outcomes. Moreover, the waiting time for a transplant is usually long, while the duration of achieved normoglycaemia remains uncertain and always transitory.

An alternative proposal based on automated glucose-controlled insulin delivery emerged 30 years ago with the development of the bedside in-hospital artificial pancreas [2-4]. This system, still used for research purposes or to cover insulin requirements under perisurgical conditions, performs continuous intravenous measurement of blood glucose while simultaneously adjusting intravenous infusions of glucose and insulin according to preset algorithms. However, medical supervision remains necessary for further adjustments to the parameters that contribute to glucose control. Also, miniaturization of the system to render it an ambulatory and autonomous treatment mode has so far failed. Nevertheless, the development of diabetes technologies has offered new perspectives over the past decade.

2. The tools necessary for closed-loop insulin delivery

Each of the three constituents of a model of an ambulatory autonomous artificial pancreas – the glucose monitoring system, the insulin delivery device and the control algorithm – are being constantly improved, as is their integration into a unified system (Fig. 1). The insulin pump is clearly the element that has achieved the highest development so far. Improvements in microelectronics have led to reliable pulsatile infusers that cause no trauma to the insulin molecule and are finely tuned for insulin delivery, and use an autonomous durable power source reduced to the size of a cell phone (portable pumps) or a hockey puck (implantable pumps). A remaining question is which infusion route to use to obtain the best kinetics of insulin action [5].

The intravenous route would be the most efficient, although it is peripheral and not portal. Unfortunately, the sustained availability of an intravenous insulin infusion remains unfeasible. The use of a central intravenous infusion was investigated in the 1990s by implantation of a subclavian catheter connected to an implanted insulin pump. The pulsatile mechanism of infusion led to unavoidable catheter obstruction by a distal clot after, at best, a few months, and sometimes extended to the vein.

The use of an intraperitoneal insulin infusion is an interesting alternative, as it allows at least partial portal insulin delivery. Also, the long-term feasibility of this option has been demonstrated by the development of implantable insulin pumps. This technology has been validated in terms of reliability of infusion and conditions for successful implantation, although it still requires improvement in three aspects. The first is the physical stability of the infused insulin. As it is exposed to body temperature, shaking conditions due to body movements and contact with materials that promote the formation of aggregates, the insulin solution, despite being combined with a stabilizing tension-active component, is still prone to physical instability, which impairs the insulin flow rate after several months. The aggregates formed in

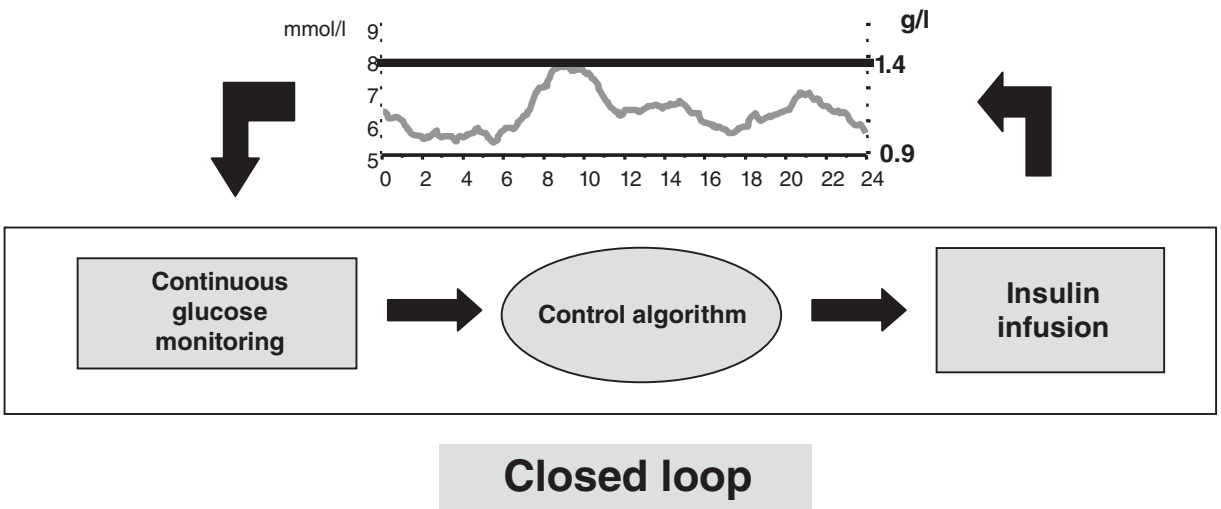

Fig. 1. The concept of the closed-loop insulin delivery system.

the pump can be solubilized and eliminated by regular rinse procedures of the pump using sodium hydroxide, but they will gradually reconstitute, leading to time-consuming management of this mode of therapy. The second problem is the eventual occurrence of obstruction in the peritoneal catheter. Although either laparoscopic clearance of the catheter or catheter replacement is feasible, each requires surgery. The third obstacle to effective insulin action is, in some cases, the development of anti-insulin antibodies that impair the kinetics of insulin action.

Thus, to summarize, although this innovative technique performs well, albeit with no alternative for patients who show unreliable absorption of subcutaneous (SC)-delivered insulin, the method requires specific medical expertise and is associated with high costs. Recent initiatives have considered the development of implantable ports that allow peritoneal insulin infusion that is easier to manage and at a reduced cost. The availability of fast-acting insulin analogues has notably improved the kinetics of SC-infused insulin, leading to reconsideration of this route of delivery as a viable option for closed-loop control with the necessary algorithmic adjustments. However, the variability of insulin action according to the individual patient and the catheter lifetime (which rarely exceeds 4 or 5 days) remain potential obstacles to reliable performance. Given to the increasingly widespread use of continuous subcutaneous insulin infusion (CSII) for diabetes treatment, this route of insulin delivery has currently been prioritized in the development of current models of ambulatory artificial pancreas.

Continuous glucose monitoring (CGM), a necessary element for closed-loop insulin delivery, has developed the most over the past decade [6]. The available technology is based on continuous glucose measurement of SC interstitial fluid by enzymatic sensors using glucose oxidase. Most CGM devices use "needle-type" sensors, implanted for 5 to 7 days in SC tissue. An alternative is based on SC microdialysis, made possible by the infusion of a buffer solution through an SC-implanted probe that "extracts" glucose from interstitial fluid to measure it in an external device where the enzyme is located. Improvements in the biocompatibility of SC sensors have allowed greater accuracy of glucose measurement during the implant time. The electrical signal generated at sensor level in proportion to SC glucose concentration is converted into an estimated blood glucose level through calibration of the signal against the current capillary blood glucose level, usually twice a day. However, there still remains a physiological delay between SC-measured and true blood glucose variations, especially when blood glucose changes rapidly. Nevertheless, an assessment of the trend to change, available online, can be taken into account by the control algorithm that modulates insulin delivery in the closed-loop mode. So far, only one CGM experiment has used intravenous enzymatic sensors, implanted through the jugular or subclavian vein, that were integrated into a fully implanted artificial pancreas system through a connection to an implanted insulin pump using intraperitoneal insulin delivery.

The control system adjusting the insulin infusion according to glucose data in the closed-loop mode is currently the part of the system that changes the most quickly [7]. Initial algorithms were "proportional-derivative" (PD), like those used for the bedside artificial pancreas. In this mode, insulin is infused according to the discrepancy between the current blood glucose level and targeted level (proportional component), and according to glucose change (derivative component). These algorithms perform effectively in models with low inertia, such as those using intravenous glucose-sensing and intravenous insulin delivery. However, if there is a delay in blood glucose estimation and, moreover, when the kinetics of insulin action are slow, such as in SC-sensing/SC-delivery models, then glucose control is significantly impaired when blood glucose changes quickly (mealtimes, physical activity). Uncontrollable glucose deviations outside of the target range result from this limited control.

The addition of an integral component into the so-called "proportional-integral-derivative" (PID) algorithms to take into account the time needed to come back into target range have not solved the problem of out-of-range glucose excursions. Neither the adjustment of parameters that modulate each of the three algorithm components according to insulin kinetics and glucose changes nor the addition of modulation of insulin infusion according to the estimated "insulin on board" have been able to effectively keep glucose within the target range when glucose levels change rapidly. This failure has led to the concept of "semi-closed-loop" control, which includes manual interventions for insulin delivery when glucose change is anticipated, such as at mealtimes.

Given the persistent failure of PID algorithms, the concept of "model predictive control" (MPC) is now under active current development. These algorithms are based on the patient's insulin sensitivity and basal daily insulin needs, and include parameters of modulation of insulin infusion according to predicted insulin action and CGM. The first experiments using these MPC algorithms have shown similar issues in the control of glucose when glucose changes quickly. The flexibility of this model of algorithm offers, however, less restricted changes to infusion parameters than do PID models. Moreover, improvements over time in a given patient because of the acquired data, as well as the online introduction of complementary information into the model (for example, a display of glucose intakes over a specific time period), have led to individualized and predictive adaptations of the algorithm. The application of "brakes" on the insulin flow rate can also be activated automatically when the system foresees harmful blood glucose decreases. Potential adaptations to this type of algorithm according to a modular approach put them currently in first place as an improvement over closed-loop algorithms.

3. Clinical investigations with autonomous artificial pancreas models

Over the past decade, the technological and algorithmic improvements mentioned above, and the sharing of

knowledge and expertise among clinicians, physiologists, modellers and engineers, have led to the establishment of partnerships and consortia that have developed various models of artificial pancreata. These models have been tested in protected clinical environments, such as at clinical research or investigative centres, thereby providing safe and continuous technical and medical supervision. Furthermore, in-silico simulations elaborated by modellers have been able to anticipate the results obtained by the developed algorithms in the preclinical phase. These simulations have replaced the animal studies that usually precede human trials, and have been made possible by previous modelling of the physiological glucose flux resulting from insulin action under various conditions (fasting, food intake, physical exercise).

Indeed, the current procedures for testing algorithms almost always include experiments *in silico* that allow adjustment of the parameters of insulin delivery according to scenarios tested on computers before being tested on humans. So far, five combinations of the different CGM systems/insulin-delivery modes/algorithm types have been investigated and reported in type 1 diabetic patients.

The first combination tested, the results of which were reported in 2001-2002, included an implanted insulin pump using the peritoneal route connected to an implanted intravenous glucose sensor that provided inputs for the control PD, and then PID, algorithms [8,9]. This fully implanted artificial pancreas model, developed by MiniMed Technologies and then by Medtronic, was dubbed the "long-term sensor system" (LTSS) and investigated from 2000 to 2007. A dozen 48 h closed-loop experiments, during which three daily meals including predefined carbohydrate intakes were offered, were performed with the LTSS. During these tests, 22-42% of the total study time was spent in tight euglycaemia (80-120 mg/dL), 5-6% of the time was spent at < 80 mg/dL, 50-60% between 120 and 240 mg/dL, and 2-10% at >240 mg/dL. Glucose control was close to normal at night and during the late post-absorption period, whereas post-meal hyperglycaemic excursions were constantly observed for several hours. Hypoglycaemia was an uncommon occurrence, seen during late post-meal periods (>2h after meal intakes) in most cases.

A few trials tested the addition of a manual premeal insulin bolus, resulting in a semi-closed-loop format. Major post-meal hyperglycaemic excursions were suppressed as well as hypoglycaemic episodes, such that 100% of the total study time was spent in the 80-240 mg/dL range, of which 35% were between 80 and 120 mg/dL. Failure to achieve permanent glucose control in the target range was mostly explained by the delay in glucose-sensing due to the internal workings of the glucose sensor. The limited operating time of the implanted sensors, close to 6 months on average, was related to the fragility of the implanted sensors, which were eroded by the shear forces of the central blood flow. Failure to improve sensor lifetime without dangerously increasing the rigidity of the implanted sensor halted the development of this particular model. Nonetheless, this first historical experiment with a fully implanted artificial pancreas model produced results that further trials, using other devices/algorithms, have only reproduced with no significantly added performance.

Subsequent investigations that combined an SC enzymatic glucose sensor, an implanted insulin pump using peritoneal delivery and an improved PID algorithm – including a component for modulation of insulin infusion according to estimated insulin levels – in a hybrid system called HyPID were carried out during 2007-2008 [10]. A premeal bolus was manually controlled. The results showed better glucose control when insulin delivery was driven by the sensor and algorithm rather than adapted by the patient according to self-monitoring of blood glucose. Time spent in normoglycaemia (80-120 mg/dL) with this closed-loop system reached 39% *vs* 28% with an open-loop mode. Outside of the immediate post-meal phases, including the 2 h following meals, mean blood glucose levels were significantly lower, and the time spent in euglycaemia reached 46% under closed-loop conditions. Although these results show the effectiveness of this specific model for glucose control, the current limitation in the development of this model lies in the currently available intraperitoneal insulin delivery devices. Also, comparative trials with SC insulin delivery are needed to identify the specific benefits related to the intraperitoneal route of insulin infusion on glucose control.

Whereas the intraperitoneal insulin delivery mode has been investigated by our research group, clinical trials have been run by Medtronic in the US combining a CGM system with CSII using fast-acting insulin analogues, linked by the same type of PID algorithms as reported above [11]. The first challenges were performed in full closed-loop mode, followed by trials of the semi-closed-loop mode, including a manual premeal bolus [12]. In the first trials, which lasted 30 h compared with 3 days of ambulatory CSII (in other words, in different environments), blood glucose was maintained at 70–180 mg/l for an average time duration of 75% *vs* 63%, respectively. Post-meal hyperglycaemic excursions limited the effectiveness of control and were sometimes followed by hypoglycaemia. When premeal boluses were added in the next reported trials, performed for 34h and also compared with ambulatory CSII, diurnal glucose control improved because of reduced post-meal glucose deviations, while nocturnal control was similar.

MPC algorithms were first applied to models including intravenous insulin infusion, followed by CSII using fast-acting analogues and continuous intravenous glucose monitoring, then simulated as SC [the ADICOL (Advanced Insulin Infusion using a Control Loop) project] and, finally, were truly SC using a microdialysis system [7]. The clinical trials ran for 8-26.5h, with or without meal intakes, and showed effective basal glucose control with no hypoglycaemia, resulting in 84-87% of the total study time spent with blood glucose levels between 60 and 170 mg/dL, and with food intakes "announced" to the system.

Recent clinical trials using MPC algorithms have also been reported using a combination of CGM and CSII [13-16]. In the first experiments, which focused on night-time control, a reduction of hypoglycaemia risk during the closed-loop phase was demonstrated even when patients had indulged in physical exercise the previous afternoon. Other challenges have since validated the effectiveness and safety of closed-loop glucose control driven by MPC algorithms under more complex conditions, such as multiple food intakes and physical exercise in hospital (data not reported except as abstracts). In addition, other models have been tested, including glucagon infusion in cases of hypoglycaemic risk [17], as well as algorithms based on clinical practice [18].

4. The way home with the artificial pancreas

The most recent experiments, mainly promoted by the initiative for an artificial pancreas funded by the JDRF, demonstrate the most likely way to move from closed-loop insulin delivery in a protected environment to home use. The step-by-step progression will probably develop according to a now clearer roadmap [19]. First, the closed-loop insulin delivery will be used at home just for the night. The fear of nocturnal hypoglycaemia will likely be mastered because the algorithms have all been shown to work, whatever the route of insulin delivery. The extension of closed-loop insulin delivery to during the day will then likely follow, as will the semi-closed-loop approach including manual management of insulin needs to cover meals and physical exercise. Automated insulin delivery after "meal announcement" will come later, when more sophisticated algorithms will be better able to manage the expected rapid blood glucose variations. At this stage, individualization of the algorithmic parameters will be necessary. One possible scenario may include the first 'hybridized', semi-closed, mode of delivery for a few days, during which time the system will acquire information on the individual characteristics of the patient. Thereafter, the patient will only have to inform the system of any forthcoming changes (meal intake, exercise activities), and the algorithm will change the parameters on its own. However, the patient's vigilance as regards blood glucose levels, which will be accessible "online", will remain mandatory to optimalize insulin delivery or in case of failure of one of the components of the closed-loop system.

Conflicts of interest statement

The authors have no conflict of interest in connection to this article.

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